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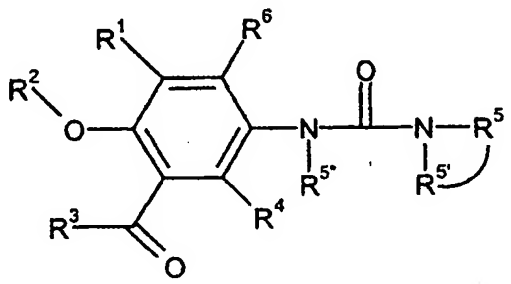
(54) BENZENE DERIVATIVES,PROCESS FOR PREPARING THE SAME AND USE THEREOF

(57) Novel benzene derivatives represented by the formula (I) :



(I)

wherein R^1, R^4 and R^6 each independently represents a hydrogen atom, a halogen atom or a hydrocarbon group, R^2 represents a hydrocarbon group or a heterocyclic group, R^3 represents a hydrocarbon group, $NR^{7'}R^7$ or OR^8 (wherein $R^{7'}$ represents a hydrogen atom or a hydrocarbon group, R^7 represents a non-aromatic group, or $R^{7'}$ and R^7 may form a ring with the adjacent nitrogen atom, and R^8 represents a hydrocarbon group or a heterocyclic group), R^5 represents a hydrocarbon group or a heterocyclic group (except for a quinolyl group), $R^{5'}$ represents a hydrogen atom, or a hydrocarbon group, or R^5 and $R^{5'}$ may form a ring with the adjacent nitrogen atom, and $R^{5''}$ represents a hydrogen atom or a hydrocarbon group, which have vanilloid receptor agonist activity and are useful as a drug such as an analgesic and an agent for preventing and/or treating urinary frequency and/or urinary incontinence.

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Description

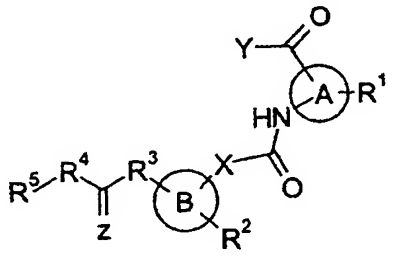
Technical Field

[0001] The present invention relates to a benzene derivative which is useful as medicines, and a preparation process and a use thereof.

Background Art

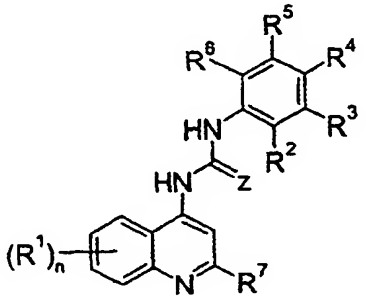
[0002] There have so far been reported on various benzene derivatives which are useful as medicines. The benzene derivatives, which contain three substituents of a urea group, a carbonyl group and an ether group on benzene ring and are useful as medicines (anticancer agents, antiobestic agents), are disclosed in e.g. WO 01/25190, WO 00/47577, and JP 63-99056 A.

[0003] That is, WO 01/25190 discloses that a compound of the formula:



wherein A and B represent an aromatic ring such as a benzene ring; COX and NHCOX are present adjacent to each other and these substituents are bonded to a carbon atom in the aromatic ring A; X represents an alkylene group, an alkyleneoxy group or a single bond; Y represents an alkyl group, an alkoxy group, a hydroxy group or a substituted or unsubstituted amino group; R^1 represents a hydrogen atom, a halogen atom, a hydroxy group or an alkyl group, etc., provided that R^1 is not hydrogen atom when A is a benzene ring; R^2 represents a hydrogen atom, a halogen atom, a hydroxy group or an alkyl group, etc.; R^3 and R^4 represent a substituted or unsubstituted imino group, an oxygen atom or a single bond; R^5 represents an alkyl group, a substituted or unsubstituted phenyl group, etc.; Z represents an oxygen atom or a sulfur atom, inhibits hyperplasia of cells.

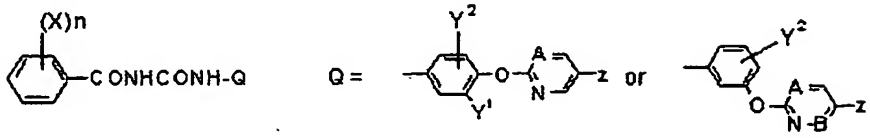
[0004] WO 00/47577 discloses that a compound of the formula:



wherein Z represents an oxygen or sulfur atom; R_1 represents a (C_{1-6})alkyl group, a (C_{2-6})alkenyl group, a (C_{1-6})alkoxy group, a halogen atom, a R^8CO group or a $NR^9R^{10}CO$ group; R^2, R^3, R^4, R^5 and R^6 each independently represents a (C_{1-6})alkyl group, a (C_{2-6})alkenyl group, a (C_{1-6})alkoxy group, a (C_{1-6})alkylthio group, a halogen atom, a hydrogen atom, a nitro group, a cyano group, an aryloxy group, an allyl(C_{1-6})alkyloxy group, an aryl(C_{1-6})alkyl group, a R^8CO group, a R^8SO_2NH group, a $R^8CON(R^{11})$ group, a NR^9R^{10} group, a $NR^9R^{10}CO$ group, a $COOR^9$ group, a heterocyclic ring or an alkyl group containing a heterocyclic ring; R^7 represents a (C_{1-6})alkyl group, a (C_{2-6})alkenyl group, a (C_{1-6}) alkoxy group, a (C_{1-6})alkythio group, a halogen atom, a hydroxy group, a nitro group, a cyano group, a NR^9R^{10} group, a $NR^9R^{10}CO$ group, a $OCOR^9$ group, a N_3 group or a $R^8CON(R^{11})$ group; R^8 represents a (C_{1-6})alkyl group or an aryl group; R^9 and R^{10} each independently represents a hydrogen atom, a (C_{1-6})alkyl group, an aryl group or an aryl(C_{1-6})

alkyl group; R^{11} represents a hydrogen atom or a (C_{1-6})alkyl group; n represents 0, 1, 2 or 3, is useful as an orexin receptor antagonist.

[0005] JP 63-99056 A discloses that a compound of the formula:



wherein, X represents a hydrogen atom, a halogen atom or a nitro group; n represents 1, 2 or 3; Y^1 represents an alkyl group, an alkoxy group or an alkoxycarbonyl group; Y^2 represents a hydrogen atom, a halogen atom, a nitro group, an alkyl group, an alkoxy group or an alkoxycarbonyl group; Z represents a hydrogen atom, a halogen atom, a trifluoromethyl group or a nitro group; either of A or B represents =CH- or N and the other represents =CH-, is useful as an anticancer agent.

[0006] In addition, capsaicin derivatives disclosed in U.S. Patent Nos. 5,099,030, 5,045,565, 5,403,868, 4,564,633, 4,544,669, 4,532,139, 4,544,668, 4,493,848, 4,460,602, 4,424,205, 4,443,473 and 4,401,663 are known as compounds having vanilloid receptor agonist activity.

[0007] U.S. Patent No. 4,313,958 discloses that capsaicin may be utilized as an analgesic agent. Further, JP 2001-513551 A discloses that resiniferatoxin may be utilized as a therapeutic agent for urinary incontinence. Still further, JP 2001-158738 A discloses capsaicinoid-like substances as an analgesic agent. WO 00/50387 also discloses benzene derivatives which are useful as medicines.

Objects of the Invention

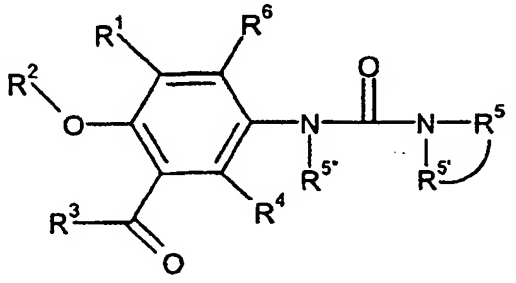
[0008] It has been desired earnestly to develop a compound that has vanilloid receptor agonist activity, and is useful as a medicine for treating acute/chronic, systemic and topical pain or inflammation, and for preventing or treating urinary frequency or urinary incontinence, etc. caused by overactivity of the bladder and cystitis. Therefore, an object of the present invention is to develop a compound which is useful as such medicine.

Summary of the Invention

[0009] The present inventors have found that a novel compound represented by the following formula (I), and characterized by containing three substituents of an urea group, a carbonyl group and an ether group on a benzene ring in chemical structure, possesses an excellent analgesic activity, a preventing and/or therapeutic activity of urinary frequency and/or urinary incontinence, and also vanilloid receptor agonist activity, and have studied extensively thereon to have completed the present invention.

[0010] That is, the present invention provides:

(1) A compound represented by the formula (I):



(I)

wherein R^1, R^4 and R^6 each independently represents a hydrogen atom, a halogen atom or an optionally substituted hydrocarbon group; R^2 represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; R^3 represents an optionally substituted hydrocarbon group, $NR^{7'}R^7$ or OR^8 (wherein $R^{7'}$ represents

a hydrogen atom or an optionally substituted hydrocarbon group, and R^7 represents an optionally substituted non-aromatic group, or $R^{7'}$ and R^7 may form an optionally substituted ring together with the adjacent nitrogen atom, and R^8 represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group); R^5 represents an optionally substituted hydrocarbon group (except for an optionally substituted benzoyl group) or an optionally substituted heterocyclic group (except for a quinolyl group); $R^{5'}$ represents a hydrogen atom, or an optionally substituted hydrocarbon group, or R^5 and $R^{5'}$ may form an optionally substituted ring together with the adjacent nitrogen atom; and $R^{5''}$ represents a hydrogen atom or an optionally substituted hydrocarbon group; or a salt thereof,

(2) The compound as described in the above (1), wherein the optionally substituted hydrocarbon group represented by R^1, R^2, R^3, R^4, R^5, $R^{5'}$, $R^{5''}$, R^6, $R^{7'}$ and R^8 each independently represents a C_{1-6}alkyl group, a C_{2-6}alkenyl group, a C_{2-6}alkynyl group, a C_{3-10}cycloalkyl group, a C_{3-10}cycloalkenyl group, a C_{4-12}cycloalkylalkyl group, a C_{4-12}cycloalkenylalkyl group, a C_{6-14}aryl group or a C_{7-19}aralkyl group, which may be independently substituted; the optionally substituted non-aromatic group represented by R^7 represents a C_{1-6}alkyl group, a C_{2-6}alkenyl group, a C_{2-6}alkynyl group, a C_{3-10} cycloalkyl group, a C_{3-10}cycloalkenyl group, a C_{4-12}cycloalkylalkyl group, a C_{4-12}cycloalkenylalkyl group, a C_{7-19}aralkyl group or a 5- to 12-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may be independently substituted; the optionally substituted heterocyclic group represented by R^2, R^5 and R^8 each independently represents a 5- to 12-membered aromatic heterocyclic group, or a saturated or unsaturated non-aromatic heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may be substituted; and the ring formed by $R^{7'}$ and R^7, and R^5 and $R^{5'}$ together with the adjacent nitrogen atom, represents an optionally substituted 3- to 12-membered nitrogen-containing heterocyclic ring which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms and one nitrogen atom,

(3) The compound as described in the above (1) or (2), wherein the substituents are 1 to 4 groups selected from a halogen atom; a nitro group; a cyano group; a hydroxy group; a mercapto group; a sulfo group; a sulfino group; a phosphono group; an optionally halogenated C_{1-6}alkyl group; an oxo group; an amidino group; an imino group; a C_{1-4}alkylenedioxy group; an optionally halogenated C_{1-6}alkoxy group; an optionally halogenated C_{1-6}alkylthio group; a carboxyl group; a formyl group; an optionally halogenated C_{1-6}alkyl-carbonyl group; a formyloxy group; an optionally halogenated C_{1-6}alkyl-carbonyloxy group; an optionally halogenated C_{1-6}alkoxy-carbonyl group; a C_{7-11}aralkyl group; a C_{7-11}aralkyloxy group; a C_{7-11}aralkyloxy-carbonyl group; a thiocarbamoyl group; an optionally halogenated C_{1-6}alkylsulfinyl group; an optionally halogenated C_{1-6alk}ylsulfonyl group; a sulfamoyl group; an optionally halogenated mono-C_{1-6}alkylsulfamoyl group; an optionally halogenated di-C_{1-6}alkylsulfamoyl group; a C_{6-10}arylsulfamoyl group; a C_{6-10}aryl group; a C_{6-10}aryloxy group; a C_{6-10}arylthio group; a C_{6-10}arylsulfinyl group; a C_{6-10}arylsulfonyl group; a C_{6-10}aryl-carbonyl group; a C_{6-10}aryl-carbonyloxy group; a group represented by the formula $-CONR^9R^{10}$ (wherein R^9 and R^{10} represents independently (1) a hydrogen atom, (2) a C_{1-6}alkyl group which may have 1 to 4 substituents selected from a halogen atom and a hydroxy group, (3) a C_{6-10}aryl group which may have 1 to 4 substituents selected from a halogen atom, a hydroxy group, and an optionally halogenated C_{1-6}alkyl group, or (4) a 5- to 12-membered heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may have 1 to 4 substituents selected from a halogen atom and an optionally halogenated C_{1-6}alkyl group, or R^9 and R^{10} may form a 3- to 8-membered nitrogen-containing heterocyclic ring together with the adjacent nitrogen atom, which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms and one nitrogen atom); a group represented by the formula $-NR^9R^{10}$ (wherein R^9 and R^{10} are as defined above); a group represented by the formula $-NHCONR^9R^{10}$ (wherein R^9 and R^{10} are as defined above); a group represented by the formula $-NR^9COR^{10}$ (wherein R^9 and R^{10} are as defined above); a group represented by the formula $-NR^9SO_2R^{10}$ (wherein R^9 and R^{10} are as defined above); and a 5- to 12-membered heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms,

(4) The compound as described in the above (1), wherein R^1 represents a hydrogen atom; R^4 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group; and R^6 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group,

(5) The compound as described in the above (1), wherein R^2 represents a C_{7-19} aralkyl group which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally

halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di-C_{6-10}arylsulfamoyl group,

(6) The compound as described in the above (1), wherein R^2 represents a C_{7-19}aralkyl group which may have 1 to 4 substituents selected from a halogen atom, an optionally halogenated C_{1-4}alkyl group, a nitro group, a cyano group, and a C_{1-4}alkoxy-carbonyl group,

(7) The compound as described in the above (6), wherein the C_{7-19}aralkyl group represents a benzhydryl group,

(8) The compound as described in the above (1), wherein R^3 represents a C_{1-4}alkyl group, a C_{1-4}alkylamino group or C_{1-4}alkoxy group,

(9) The compound as described in the above (1), wherein R^5 represents a C_{6-10}aryl group, a pyridyl group or a C_{7-11}aralkyl group, each of which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-$C_{6-10ary}$lsulfamoyl group, and a di-C_{6-10}arylsulfamoyl group,

(10) The compound as described in the above (1), wherein R^5 represents a phenyl group which may have 1 or 2 C_{1-4}alkoxy groups,

(11) The compound as described in the above (1), wherein R^1 represents a hydrogen atom; R^2 represents a C_{7-19} aralkyl group which may have 1 to 4 substituents selected from a halogen atom, an optionally halogenated C_{1-4}alkyl group, a nitro group, a cyano group, and a C_{1-4}alkoxycarbonyl group; R^3 represents a C_{1-4}alkyl group, a C_{1-4}alkylamino group or C_{1-4}alkoxy group; R^4 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group; R^5 represents a C_{6-10}aryl group, a pyridyl group or a C_{7-11} aralkyl group, each of which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkylcarbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxycarbonyl group, an optionally halogenated C_{1-6}alkylthiocarbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di C_{6-10}arylsulfamoyl group; and R^6 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group,

(12) The compound as described in the above (1), wherein $R^{5'}$, $R^{5''}$, and $R^{7'}$ represent independently a hydrogen atom,

(13) The compound as described in the above (1), which is N-(4-benzhydryloxy-3-isobutyrylphenyl)-N'-(3,4-dimethoxyphenyl)urea,

methyl 5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-fluorophenyl)(phenyl)methoxy]benzoate,

methyl 5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate,

methyl 5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4'-chlorophenyl)methoxy]benzoate,

N-(tert-butyl)-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy}benzamide,

methyl 2-[(3,4-difluorophenyl)(phenyl)methoxy]-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate,

methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate,

N-(tert-butyl)-2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy)-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide,

N-(tert-butyl)-2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide,

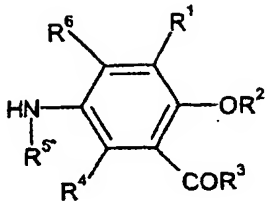
N-(tert-butyl)-2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide, or

N-(tert-butyl)-2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide.

(14) A prodrug of the compound as described in the above (1) or a salt thereof,

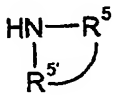
(15) A process for preparing a compound as described in the above (1) or a salt thereof, which comprises subjecting

a compound represented by the formula:

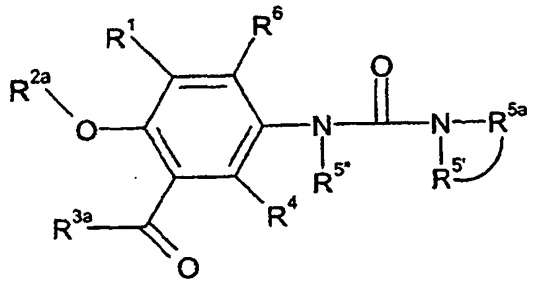


(II)

wherein each symbol is as defined in the above (1), or a salt thereof and a compound represented by the formula:



wherein each symbol is as defined in the above (1), or a salt thereof to urea synthesis reaction,
(16) A pharmaceutical composition comprising the compound of the above (1), a pharmaceutically acceptable salt or a prodrug thereof,
(17) A vanilloid receptor agonist comprising a compound represented by the formula:



(Ia)

wherein R^1, R^4 and R^6 each independently represents a hydrogen atom, a halogen atom or an optionally substituted hydrocarbon group; R^{2a} represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; R^{3a} represents an optionally substituted hydrocarbon group, $NR^{7'}R^{7a}$ or OR^8 (wherein $R^{7'}$ represents a hydrogen atom or an optionally substituted hydrocarbon group, R^{7a} and R^8 represent independently an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or $R^{7'}$ and R^{7a} may form an optionally substituted ring together with the adjacent nitrogen atom); R^{5a} represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, and $R^{5'}$ represents a hydrogen atom, or an optionally substituted hydrocarbon group, or R^{5a} and $R^{5'}$ may form an optionally substituted ring together with the adjacent nitrogen atom; and $R^{5''}$ represents a hydrogen atom or an optionally substituted hydrocarbon group], a pharmaceutically acceptable salt or a prodrug thereof,
(18) An agent for preventing and/or treating urinary frequency and/or urinary incontinence, which comprises the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof,
(19) An analgesic agent which comprises the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof,
(20) Use of the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof for manufacturing an agent for preventing and/or treating urinary frequency and/or urinary incontinence,
(21) Use of the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof for manufacturing an analgesic agent,
(22) Use of the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof for manufacturing a vanilloid receptor agonist,

(23) A method for preventing and/or treating urinary frequency and/or urinary incontinence, which comprises administrating to a mammal an effective amount of the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof, and

(24) An analgesic method which comprises administrating to a mammal an effective amount of the compound of the formula (Ia) as described in the above (17), a pharmaceutically acceptable salt or a prodrug thereof.

Detailed Description of the Invention

[0011] In the above-mentioned formula (I), as the halogen atom represented by R^1, R^4 and R^6, for example, fluorine, chlorine, bromine, iodine, and the like may be used.

[0012] Examples of the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 include an aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an alicyclic-aliphatic hydrocarbon group and an aromatic hydrocarbon group, and carbon number of these groups is preferably 1 to 16. Specifically, for example, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkenyl group, a cycloalkylalkyl group, a cycloalkenylalkyl group, an aryl group, an aralkyl group, and the like are used.

[0013] Examples of the "alkyl group" include preferably a lower alkyl group, for example, a C_{1-6}alkyl group, etc. such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpropyl, hexyl, etc.

[0014] Examples of the "alkenyl group" include preferably a lower alkenyl group, for example, a C_{2-7}alkenyl group, etc. such as vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, 2,2-dimethyl-pent-4-enyl, etc.

[0015] Examples of the "alkynyl group" include preferably a lower alkynyl group, for example, a C_{2-6}alkynyl group, etc. such as ethynyl, propargyl, 1-propynyl, etc.

[0016] Examples of the "cycloalkyl group" include preferably a lower cycloalkyl group, for example, a C_{3-10}cycloalkyl group, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptanyl, adamanthyl, etc.

[0017] Examples of the "cycloalkenyl group" include preferably a lower cycloalkenyl group, for example, a C_{3-6}cycloalkenyl group, etc. such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, etc.

[0018] Examples of the "cycloalkylalkyl group" include preferably a lower cycloalkylalkyl group, etc., for example, a C_{4-12}cycloalkylalkyl group, etc. such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl, etc.

[0019] Examples of the "cycloalkenylalkyl group" include preferably a lower cycloalkenylalkyl group, etc., for example, a C_{4-12}cycloalkenylalkyl group, etc. such as cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cyclohexenylpropyl, cycloheptenylmethyl, cycloheptenylethyl, bicyclo[2.2.1]hept-5-en-2-ylmethyl, etc.

[0020] Examples of the "aryl group" include preferably a C_{6-14}aryl group, etc. such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc., for example, phenyl may be used.

[0021] Examples of the "aralkyl group" include preferably a C_{7-19}aralkyl group, etc. such as benzyl, benzhydryl, 1,1'-biphenyl-4-ylmethyl, 3,3-diphenylpropyl, 3-phenylpropa-2-enyl, phenylethyl, phenylpropyl, etc., for example, benzyl, benzhydryl, etc. may by used.

[0022] In addition, examples of the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 include a group formed by fusion of a cycloalkyl group in the above "cycloalkyl group" or "cycloalkylalkyl group" with a benzene ring (e.g., a polycyclic hydrocarbon group such as indanyl, etc.).

[0023] Examples of the substituents that the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 may have, include a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a nitro group, a cyano group, a hydroxy group, a mercapto group, a sulfo group, a sulfino group, a phosphono group, an optionally halogenated C_{1-6}alkyl group (e.g., a C_{1-6}alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, etc.; a mono-, di- or tri-halogeno-C_{1-6}alkyl group, etc. such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, 6,6,6-trifluorohexyl, etc.), an oxo group, an amidino group, an imino group, an alkylenedioxy group (e.g., a C_{1-4}alkylenedioxy group, etc. such as methylenedioxy, ethylenedioxy, etc.), an optionally halogenated C_{1-6}alkoxy group (e.g., a C_{1-6}alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy etc.; a mono-, di- or tri-halogeno-C_{1-6}alkoxy group, etc. such as trifluoromethoxy, etc.), an optionally halogenated C_{1-6}alkylthio group (e.g., a C_{1-6}alkylthio group such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio, etc.; a mono-, di- or tri-halogeno-C_{1-6}alkylthio group, etc. such as of trifluoromethylthio, etc.), a carboxyl group, a formyl group, an optionally halogenated C_{1-6}alkyl-carbonyl group (e.g., a C_{1-6}alkyl-carbonyl group, etc. such as acetyl, propionyl, butyryl, isobutyryl, etc.), a formyloxy group, an optionally halogenated C_{1-6}alkyl-carbonyloxy group (e.g., a C_{1-6}alkyl-carbonyloxy group, etc. such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an optionally halogenated C_{1-6}alkoxycarbonyl group (e.g., a C_{1-6}alkoxy-carbonyl, etc. such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a C_{7-11}aralkyl group (benzyl, etc.), a C_{7-11}aralkyloxy group (benzyloxy, etc.), an aralkyloxycarbonyl group (e.g., a C_{7-11}aralkyloxy-carbonyl, etc. such as

benzyloxycarbonyl, etc.), a thiocarbamoyl group, an optionally halogenated C_{1-6}alkylsulfinyl group (e.g., a C_{1-6}alkylsulfinyl group such as methylsulfinyl, ethyl sulfinyl, etc.), an optionally halogenated C_{1-6}alkylsulfonyl group (e.g., a C_{1-6}alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, etc.), a sulfamoyl group, optionally halogenated mono-alkylsulfamoyl group (e.g., mono-C_{1-6}alkylsulfamoyl group, etc. such as methylsulfamoyl, ethylsulfamoyl, etc.), an optionally halogenated di-alkyl sulfamoyl group (e.g., a di-C_{1-6}alkylsulfamoyl group, etc. such as dimethylsulfamoyl, diethylsulfamoyl, etc.), an arylsulfamoyl group (e.g., a C_{6-10}arylsulfamoyl group, etc. such as phenylsulfamoyl, naphthylsulfamoyl, etc.), an aryl group (e.g., a C_{6-10}aryl group, etc. such as phenyl, naphthyl, etc.), an aryloxy group(e.g., a C_{6-10}aryloxy group, etc. such as phenyloxy, naphthyloxy, etc.), an arylthio group (e.g., a C_{6-10}arylthio group, etc. such as phenylthio, naphthylthio, etc.), an arylsulfinyl group (e.g., a C_{6-10}arylsulfinyl group such as phenylsulphinyl, naphthylsulfinyl, etc.), an arylsulfonyl group (e.g., a C_{6-10}arylsulfonyl group, etc. such as phenylsulfonyl, naphthylsulfonyl, etc.), an arylcarbonyl group (e.g., a C_{6-10}aryl-carbonyl group, etc. such as benzoyl, naphthoyl, etc.), an arylcarbonyloxy group (e.g., a C_{6-10}aryl-carbonyloxy group, etc. such as benzoyloxy, naphthoyloxy, etc.), an optionally substituted carbamoyl group [e.g., a group represented by the formula $-CONR^9R^{10}$ (wherein R^9 and R^{10} each independently represents (1) a hydrogen atom, (2) a C_{1-6}alkyl group which may have 1 to 4 substituents selected from a halogen atom and a hydroxy group, (3) a C_{6-10}aryl group which may have 1 to 4 substituents selected from a halogen atom, a hydroxy group, and an optionally halogenated C_{1-6}alkyl group, or (4) a 5-to 12-membered heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may have 1 to 4 substituents selected from a halogen atom and an optionally halogenated C_{1-6}alkyl group, or R^9 and R^{10} may form a 3- to 8-membered nitrogen-containing heterocyclic ring, which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms and one nitrogen atom, together with the adjacent nitrogen atom (e.g., they may form a 3- to 8-membered (preferably, a 5-to 6-membered) nitrogen-containing heterocyclic ring such as aziridine, azetidine, pyrrolidine, pyrroline, pyrrole, imidazole, pyrazoline, imidazolidine, piperidine, morpholine, dihydropyridine, pyridine, piperazine, etc.)], an optionally substituted amino group (e.g., a group represented by the formula $-NR^9R^{10}$ (wherein R^9 and R^{10} are as defined above), an optionally substituted ureido group (e.g., a group represented by the formula $-NHCONR^9R^{10}$ wherein R^9 and R^{10} are as defined above), an optionally substituted carboxamide group (e.g., a group represented by the formula $-NR^9COR^{10}$ wherein R^9 and R^{10} are as defined above), an optionally substituted sulfonamide group (e.g., a group represented by the formula $-NR^9SO_2R^{10}$ wherein R^9 and R^{10} are as defined above), an optionally substituted heterocyclic group, and the like.

[0024] Examples of the "optionally substituted hydrocarbon group" in the substituents that the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 may have, include those as mentioned above, but when the substituents have a hydrocarbon group as a substituent, the hydrocarbon group is unsubstituted.

[0025] Examples of the "heterocyclic group" in the "optionally substituted heterocyclic group" represented by R^1, R^4 and R^6 include a 5- to 12-membered monocyclic or fused heterocyclic group, etc. containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, such as pyridyl, pyrrolidinyl, piperazinyl, piperidinyl, 2-oxoazepinyl, furyl, decahydroisoquinolyl, quinolinyl, indolyl, isoquinolyl, thienyl, imidazolyl, morpholyl, etc. Examples of the "substituents" that the "optionally substituted heterocyclic group" may have, include the "substituents" in the "optionally substituted heterocyclic group" represented by R^2 which will be described below, but when the substituent is a heterocyclic group or a hydrocarbon group having a heterocyclic group, the heterocyclic group is unsubstituted.

[0026] Preferably, R^1 represents a hydrogen atom, R^4 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group (e.g., methyl, ethyl, isopropyl, tert-butyl, etc.), and R^6 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group (e.g., methyl, ethyl, isopropyl, tert-butyl, etc.).

[0027] As the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by R^2, for example, those for the "hydrocarbon group" in the "optionally substituted hydrocarbon group" represented by the above-mentioned R^1, R^4 and R^6, preferably, an alkyl group, an alkenyl group and an alkynyl group may be used. As the "substituents", those for the "substituents" in the "optionally substituted hydrocarbon group" represented by the above-mentioned R^1, R^4 and R^6, may be used.

[0028] Examples of the "optionally substituted hydrocarbon group" represented by R^2, include preferably an optionally substituted C_{7-19}aralkyl group, particularly, an optionally substituted benzyl group, or an optionally substituted benzhydryl group. As R^2, an unsubstituted benzhydryl group, a 4-tert-butylbenzyl group, a 4-isopropylbenzyl group, etc is preferable.

[0029] Examples of the "optionally substituted heterocyclic group" represented by R^2, include a 5- to 12-membered aromatic heterocyclic group, or a saturated or unsaturated non-aromatic heterocyclic group, etc. which contains at least 1 hetero atom (preferably 1 to 4 hetero atoms, more preferably 1 to 2 hetero atoms) consisting of 1 to 3 kinds of hetero atoms (preferably 1 to 2 kinds of hetero atoms) selected from an oxygen atom, a sulfur atom, a nitrogen atom, etc. as ring-constituting atoms.

[0030] Examples of the "aromatic heterocyclic group" include an aromatic monocyclic heterocyclic group or an aro-

matic fused heterocyclic grop, etc.

[0031] Examples of the "aromatic monocyclic heterocyclic group" include a 5- to 6-membered aromatic monocyclic heterocyclic group, etc. such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl. etc.

[0032] Examples of the "aromatic fused heterocyclic group" include a 8- to 12-membered aromatic fused heterocyclic group (preferably, a heterocyclic group formed by fusion of the above-mentioned 5- or 6-membered aromatic monocyclic heterocyclic group with a benzene ring or a heterocyclic group formed by fusion of two above-mentioned 5- or 6-membered aromatic monocyclic heterocyclic groups which are the same or different) etc. such as benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, etc.

[0033] Examples of the "saturated or unsaturated non-aromatic heterocyclic group" include a 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group (alicyclic heterocyclic group), etc. such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, thianyl, morpholyl, thiomorpholyl, piperazinyl, azepanyl, oxepanyl, thiepanyl, oxazepanyl, thiazepanyl, azocanyl, oxocanyl, thiocanyl, oxazocanyl, thiazocanyl, etc. These may be substituted with oxo, for example, may be 2-oxoazetidinyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoazepanyl, 2-oxoazocanyl, 2-oxotetrahydrofuryl, 2-oxotetrahydropyranyl, 2-oxothiolanyl, 2-oxothianyl, 2-oxopiperazinyl, 2-oxooxepanyl, 2-oxooxazepanyl, 2-oxothiepanyl, 2-oxothiazepanyl, 2-oxoazocanyl, 2-oxooxocanyl, 2-oxothiocanyl, 2-oxooxazocanyl, 2-oxothiazocanyl, and the like, preferably a 5-membered non-aromatic heterocyclic group such as 2-oxopyrrolidinyl, etc.

[0034] Examples of the "heterocyclic group" in the "optionally substituted heterocyclic group" represented by R^2, include preferably a 5- to 7-membered (preferably 5- or 6-membered, more preferably 5-membered) aromatic heterocyclic group which contains 1 to 3 (preferably 1 or 2) hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, particularly a pyridyl group.

[0035] As the substituents that the "heterocyclic group" in the "optionally substituted heterocyclic group" represented by R^2 may have, for example, those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above may be used.

[0036] The "heterocyclic group" in the "optionally substituted heterocyclic group" represented by R^2 may have 1 to 5, preferably 1 to 3 substituents as described above at any possible position on the heterocyclic group, and when the number of the substituents is 2 or more, each substituent may be the same or different.

[0037] R^2 is preferably a C_{7-19}aralkyl group which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di-C_{6-10}arylsulfamoyl group.

[0038] R^2 is more preferably a C_{7-19}aralkyl group (a benzhydryl group, etc.) which may have 1 to 4 substituents selected from a halogen atom, an optionally halogenated C_{1-4}alkyl group, a nitro group, a cyano group and a C_{1-4}alkoxycarbonyl group.

[0039] R^3 represents an optionally substituted hydrocarbon group, $NR^{7'}R^7$ or OR^8, and as the "optionally substituted hydrocarbon group" represented by R^3, those for the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above may be used. Particularly, an optionally halogenated C_{1-4}alkyl group is preferred.

[0040] $R^{7'}$ in $NR^{7'}R^7$ represents the "hydrogen atom or optionally substituted hydrocarbon group", and as the "optionally substituted hydrocarbon group", those for the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above may be used. As the substituents, those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above may be used. R^7 represents a " optionally substituted non-aromatic group ", and as the "non-aromatic group", the aliphatic hydrocarbon group, the alicyclic hydrocarbon group, the alicyclic-aliphatic hydrocarbon group, non-aromatic heterocyclic group, and the like as described above (for example, a C_{1-6}alkyl group, a C_{2-6}alkenyl group, a C_{2-6}alkynyl group, a C_{3-10}cycloalkyl group, a C_{3-10}cycloalkenyl group, a C_{4-12}cycloalkylalkyl group, a C_{4-12}cycloalkenylalkyl group, a C_{7-19}aralkyl group, or a 5- to 12-membered non-aromatic heterocyclic group that contains 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may have

independently a substituent) may be used. As the substituents, those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above may be used. As R^7, an optionally halogenated C_{1-4}alkyl group is preferred and as $R^{7'}$, a hydrogen atom is preferred.

[0041] Further, $R^{7'}$ and R^7 may form an "optionally substituted ring" together with the adjacent nitrogen atom, and examples of the "optionally substituted ring" includes a "3- to 12-membered nitrogen-containing heterocyclic ring", etc. which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms and one nitrogen atom. Specific examples of the "3- to 12-membered nitrogen-containing heterocyclic ring" include a non-aromatic heterocyclic ring such as aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneimine, heptamethyleneimine, morpholine, thiomorpholine, pyrazolidine, piperazine, etc., an aromatic heterocyclic ring, etc. such as pyrazole, pyridine, quinoline, isoquinoline, pyrazine, pyrimidine, pyrrole, imidazole, pyridazine, isothiazoline, oxazole, isoxazole, indole. etc.

[0042] In addition, examples of the substituents in the "optionally substituted ring" include those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above.

[0043] R^8 in OR^8 represents the "optionally substituted hydrocarbon group" or the "optionally substituted heterocyclic group", and as the "optionally substituted hydrocarbon group" and the "optionally substituted heterocyclic group", those for the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above, or those for the "optionally substituted heterocyclic group" represented by R^2 as described above may be used. As R^8, particularly, an optionally halogenated C_{1-4}alkyl group is preferred.

[0044] R^3 is preferably a C_{1-4}alkyl group, a C_{1-4}alkylamino group or a C_{1-4}alkoxy group.

[0045] R^5 represents an "optionally substituted hydrocarbon group (except for an optionally substituted benzoyl group)" or a "optionally substituted heterocyclic group (except for a quinolyl group)". As these groups, those for the "optionally substituted hydrocarbon group" (except for an optionally substituted benzoyl group) represented by R^1, R^4 and R^6 as described above or those for the "optionally substituted heterocyclic group" (except for a quinolyl group) represented by R^2 as described above, may be used. As R^5, particularly, an optionally substituted phenyl group, or an optionally substituted pyridyl group is preferred.

[0046] R^5 is preferably a C_{6-10}aryl group, a pyridyl group or a C_{7-11}aralkyl group, each of which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di C_{6-10}arylsulfamoyl group, more preferably, a phenyl group that may have 1 or 2 C_{1-4}alkoxy groups.

[0047] $R^{5'}$ represents the "hydrogen atom or optionally substituted hydrocarbon group", and examples of the "optionally substituted hydrocarbon group" includes those for the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above. As the substituents, those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above may be used.

[0048] Further, R^5 and $R^{5'}$ may form an "optionally substituted ring" together with the adjacent nitrogen atom, and examples of the "optionally substituted ring", includes a "3- to 12-membered nitrogen-containing heterocyclic ring", etc. which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms and one nitrogen atom. Examples of the "3-to 12-membered nitrogen-containing heterocyclic ring" include those for the "optionally substituted ring" formed by $R^{7'}$ and R^7 as described above together with the adjacent nitrogen atom. In addition, examples of the substituents in the "optionally substituted ring" include those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above.

[0049] $R^{5''}$ represents the "hydrogen atom or optionally substituted hydrocarbon group", and examples of the "optionally substituted hydrocarbon group" include those for the "optionally substituted hydrocarbon group" represented by as described above R^1, R^4 and R^6. Examples of the substituents include those for the "substituents" in the "optionally substituted hydrocarbon group" represented by R^1, R^4 and R^6 as described above.

[0050] As $R^{5'}$ and $R^{5''}$, a hydrogen atom is preferable.

[0051] The compound represented by the formula (I) of the present invention is preferably the compound wherein R^1 represents a hydrogen atom; R^2 represents a C_{7-19}aralkyl group which may have 1 to 4 substituents selected from a halogen atom, an optionally halogenated C_{1-4}alkyl group, a nitro group, a cyano group and a C_{1-4}alkoxy-carbonyl group; R^3 represents a C_{1-4}alkyl group, a C_{1-4}alkylamino group or a C_{1-4}alkoxy group; R^4 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group; R^5 represents a C_{6-10}aryl group, a pyridyl group or a C_{7-11ar}alkyl group, each of which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group,

a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di-C_{6-10}arylsulfamoyl group; and R^6 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group.

[0052] Examples of the salt of the compound represented by the formula (I) include an acid addition salt such as an inorganic acid salt (e.g., hydrochloride, sulfate, hydrobromide, phosphate, etc.), an organic acid salt (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartarate, lactate, oxalate, methanesulfonate, benzensulfonate, p-toluenesulfonate, etc.), as well as a salt with a base, such as an alkali metal salt (e.g., potassium salt, sodium salt, lithium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, a salt with an organic base (e.g., trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt, quinoline salt). Among others, a pharmaceutically acceptable salt is preferable.

[0053] In addition, the compound represented by the formula (I) or a salt thereof may be in the form of a hydrate or a solvate. Hereinafter, the compound including a salt thereof, a hydrate thereof and a solvate thereof will be also referred to as the compound (I).

[0054] The prodrug of the compound (I) means a compound which is converted to the compound (I) by a reaction with an enzyme, a gastric acid, etc. in a living body.

[0055] Examples of the prodrug of the compound (I) include a compound wherein if the compound (I) has an amino group, the amino group of the compound (I) is acylated, alkylated, or phosphorylated, (for example, a compound wherein the amino group of the compound (I) is substituted with eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, or tert-butyl, etc.); a compound wherein if the compound (I) has a hydroxy group, the hydroxyl group of the compound (I) is acylated, alkylated, phosphorylated, or substituted with boric acid, (for example, a compound wherein the hydroxyl group of the compound (I) is substituted with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, or dimethylaminomethylcarbonyl, etc.); a compound wherein if the compound (I) has a carboxyl group, the carboxyl group of the compound (I) is esterified or amidated, (for example, a compound wherein the carboxyl group is modified with ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, or methylamide); and the like. These compounds can be produced from the compound (I) according to a per se known method. Also, the prodrug of compound (I) may be a compound which is converted into the compound (I) under the physiological conditions as described in "Development of Drugs", vol. 7, Molecular Design, pp. 163-198 published in 1990 by Hirokawa Publishing Company.

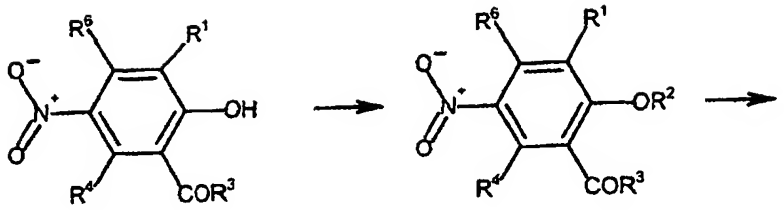
[0056] The prodrug of the compound (I) may be itself or a pharmaceutically acceptable salt thereof. In case that the prodrug of the compound (I) has an acidic group such as a carboxyl group, etc., the examples of these salts include salts with an inorganic base such as an alkali metal (e.g., sodium, potassium, and the like), an alkaline earth metal (calcium, magnesium, and the like), a transition metal, etc. (e.g., zinc, iron, copper, and the like), salts with an organic base such as organic amines (e.g., trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, and the like), basic amino acids (e.g., arginine, lysine, ornithine, and the like), and so on.

[0057] In case that the prodrug of the compound (I) has a basic group such as an amino group, etc., examples of the salts include salts with an inorganic acid or organic acid (e.g., hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, carbonic acid, bicarbonic acid, formic acid, acetic acid, propionic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like), an acidic amino acid (e.g., aspartic acid, glutamic acid, and the like), and so on.

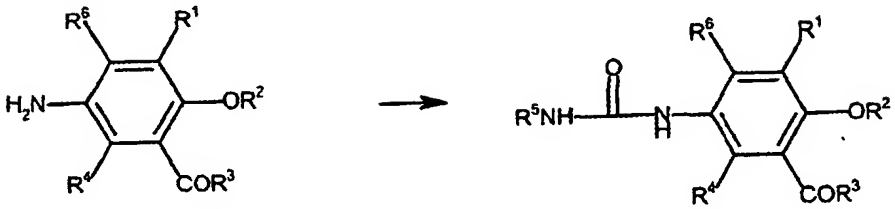
[0058] The prodrug of the compound (I) may be in any form of hydrate or non-hydrate.

[0059] The compound (I) may contain one or more asymmetric carbon atoms in the molecule and the compounds having any one of R configuration and S configuration relating to the asymmetric carbon atoms are included in the scope of the present invention.

[0060] The compound (I) can be produced by, for example, the following preparation process 1:



IV III



II I

wherein each symbol is as defined above, or an analogous process thereto.

[0061] According to the process 1, first, a compound (IV) is subjected to alkylation to produce a compound (III).

[0062] The alkylation is carried out in the presence of a base and an alkyhalide in a solvent having no influence on the reaction, in accordance with a conventional method. Examples of the base include potassiun carbonate, sodium carbonate, sodium hydride, potassium hydride, and the like.

[0063] Examples of the alkylhalide include alkyl chloride, alkyl bromide, alkyl iodide, alkyl methanesulfonate, and the like.

[0064] The amounts of the base and the alkylhalide to be used are preferably about 1 to 5 molar equivalents to the compound (IV), respectively.

[0065] Examples of the solvent having no influence on the reaction include ethers such as tetrahydrofuran, etc.; halogenated hydrocarbons such as chloroform, etc.; aromatic hydrocarbons such as toluene, etc.; amides such as N, N-dimethylformamide, etc.; sulfoxides such as dimethylsulfoxide, etc.; or the like. These solvents may be used by mixing two or more solvents in an appropriate ratio. The amount of the solvent to be used is, for example, 1 to 100 times the volume of the compound (IV).

[0066] The reaction temperature is usually about -50 to about 250°C, preferably about 0°C to about 120°C.

[0067] The reaction time is usually about 0.5 to about 24 hours. The compound (III) thus produced may be isolated and purified through any known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, or the like. In addition, the compound (III) may be used without isolation in the subsequent reaction step.

[0068] Then, the compound (III) is subjected to reduction to produce the compound (II).

[0069] This reaction is carried out by using a reducing agent in a solvent having no influence on the reaction, in accordance with a conventional method.

[0070] Examples of the solvent having no influence on the reaction include alcohols such as methanol, etc.; ethers such as tetrahydrofuran, etc.; hydrocarbons such as ethyl acetate, etc.; water; or the like. These solvents may be used by mixing 2 or more solvents in an appropriate ratio. The amount of the solvent to be used is, for example, 1 to 100 times the volume of the compound (III).

[0071] Examples of the reducing agent include hydrogen in the presence of iridium carbon, sodium hydrosulfite, hydrogen iodide, or the like. The amount of the reducing agent to be used is preferably 1 to 100 molar equivalents.

[0072] The reaction temperature is usually about -50 to 200°C.

[0073] The reaction time is usually about 0.5 to 24 hours.

[0074] The compound (II) thus produced may be isolated and purified through any known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystalliza-

tion, phase transfer, chromatography, or the like. In addition, the compound (II) may be used in the subsequent reaction step without isolation.

[0075] Then, the compound (II) is subjected to the urea synthesis reaction to produce the compound (I).

[0076] This reaction is carried out by using an urea formation agent in a solvent having no influence on the reaction, in accordance with a conventional method.

[0077] Examples of the urea formation agent include phenyl isocyanate, 3,4-dimethoxyphenyl isocyanate, 3-methoxyphenyl isocyanate, 4-methoxyphenyl isocyanate, or the like. In addition, the urea formation agent also includes a reagent formed in a reaction system by reacting a carbonylating agent in the presence of an appropriate amine, and then the reagent as such is reacted with the compound (II). Examples of the carbonylating agent include carbonyldiimidazole, phosgene, di(N-succinimidyl) carbonate, or the like. The amount of the urea formation agent to be used is preferably about 1 to 5 molar equivalents, relative to the compound (II).

[0078] Examples of the solvent having no influence on the reaction include ethers such as tetrahydrofuran, etc.; halogenated hydrocarbons such as chloroform, etc.; aromatic hydrocarbons such as toluene, etc.; amides such as N, N-dimethylformamide, etc.; sulfoxides such as dimethylsulfoxide, etc; or the like. These solvents may be used by mixing 2 or moresolvents in an appropriate ratio. The amount of the solvent to be used is 1 to 100 times the volume of the compound (II).

[0079] The reaction temperature is usually about -50 to about 250°C, preferably about 0°C to 120°C.

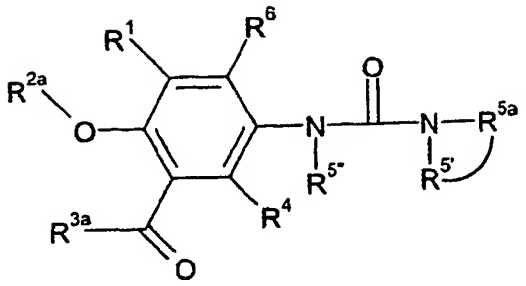
[0080] The reaction time is usually about 0.5 to 24 hours.

[0081] The compound (I) thus produced may be isolated and purified through any known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, or the like.

[0082] The compound (IV) to be used as a starting compound is commercially available, or can be prepared by per se known processes such as the processes described in "Bulletin of the Chemical Society of Japan", vol. 56, pp. 2762-2763 (1983), "Journal of Medicinal Chemistry", vol. 37, pp. 845-859 (1994), JP 5-294920 A, and the like or analogous processes thereof.

[0083] The compound (I) of the present invention and a prodrug thereof possess an excellent analgesic action, a preventing and/or therapeutic action of urinary frequency and/or urinary incontinence, and a pharmaceutical composition comprising them is useful as an analgesic agent, and an agent for preventing and/or treating urinary frequency and/or urinary incontinence, and the like. Therefore, the pharmaceutical composition is useful for treating acute/chronic, systemic and topical pain and/or inflammation, for example, treatment of gonarthritis, arthralgia such as lumbago, osteoarthritis, chronic articular rheumatism, fibromyalgia, Guillain-Barre syndrome, meralgia paraesthetica, pain by reflex sympathetic dystrophy syndrome, postoperative pain, diabetic neuralgia, herpes zoster pain, cancer pain, migraine, muscle pain, dental pain, myocardial infarction, reflex sympathetic nerve anomaly symptom, pain by trigeminal neuralgia, postmastectomy pain; analgesia for pain, etc. by burns; treatment of pain by inflammatory digestive system disease and enterokinesis; treatment of allergic rhinitis and vasomotor rhinitis; treatment of atopic dermatitis, psoriasis, lichen simplex chronicus, hemodialysis, itch by rash, etc.; treatment of urinary frequency and/or urinary incontinence by overactive bladder and cystitis; or the like. In addition, the pharmaceutical composition is also useful for treatment of clamacteric disorders, or flush or glow by administration of gonadotrophin agonist; treatment of emesis by antiemetic or anticancer drug; prevention of obesity; inhibition of fat accumulation (fat metabolism enhancer); lowering cholesterol; enhancing secretion of adrenaline (increasing action of cardiac rate, etc.); lowering blood pressure; protection of gastric mucosa; enhancing secretion of saliva or stomach juice; lowering blood glucose; treatment of irritable bowel syndrome; treatment of toxic shock, septic shock, arterial sclerosis, cancer; prevention of progress of nerve tissue degenerative disease such as cerebral apoplexy (cerebral infarction, cerebral hemorrhage); prevention and/or treatment of motor neuron disease, Parkinson's disease, Alzheimer's disease, AIDS-associated dementia, Lewy body disease, cerebral neuropathy, peripheral neuropathy and prion disease.

[0084] In addition, the present inventors have found that a compound represented by the formula:



(Ia)

wherein R^{2a} represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; R^{3a} represents an optionally substituted hydrocarbon group, $NR^{7'}R^{7a}$ or OR^8 (wherein $R^{7'}$ represents a hydrogen atom or an optionally substituted hydrocarbon group, R^{7a} and R^8 each independently represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or $R^{7'}$ and R^{7a} may form an optionally substituted ring together with the adjacent nitrogen atom); R^{5a} represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; $R^{5'}$ represents a hydrogen atom, or an optionally substituted hydrocarbon group, or R^{5a} and $R^{5'}$ may form an optionally substituted ring together with the adjacent nitrogen atom; $R^{5''}$ represents a hydrogen atom or an optionally substituted hydrocarbon group, R^1, R^4 and R^6 are as defined in the above-described formula (I), and the "optionally substituted hydrocarbon group", the "optionally substituted heterocyclic group" and the "ring formed together with the adjacent nitrogen atom" are as defined in the above-described formula (I), or a salt thereof (hereinafter, referred to as a compound (Ia)) including the compound (I) possess vanilloid receptor agonist activity.

[0085] Therefore, the present invention also provides a vanilloid receptor agonist comprising the compound (Ia) or a prodrug thereof.

[0086] The vanilloid receptor is a nociceptor which mediates pain, and an agonist thereof has the effect of desensitizing nerves. Therefore, the vanilloid receptor agonist of the present invention is an analgesic agent or an agent for preventing and/or treating urinary frequency and/or urinary incontinence, and useful for the prevention and/or treatment of diseases and disorders as described above.

[0087] The compound (I) or the compound (Ia) of the present invention may be administered orally or parenterally, and are particularly suitable for oral administration because they have no pungent taste. Further, these compounds can be used for the prevention and/or treatment of the above-mentioned diseases and disorders by formulating into forms suitable for the administration.

[0088] The compound (I) or the compound (Ia) of the present invention may be used in combination with other drugs for the prevention and/or treatment of diseases and disorders (e.g., other drugs for the prevention and/or treatment of central nervous system diseases).

[0089] The compound (I) or (Ia) has a low toxicity and can be safely administered orally or parenterally (e.g., topical, rectal, intravenous administration, etc.) as such or as a pharmaceutical composition, which is produced by compounding with a pharmaceutically acceptable carrier according to a per se known method, in the form of tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), solutions, injectable preparations, nasal drops, suppositories, sustained-release formulations, plasters, chewing gums, or the like.

[0090] The content of the compound (I) or (Ia) in the formulation of the present invention is about 0.01 to about 100% by weight based on the total weight of the formulation. The dosage may vary depending on the administration subject, the administration route, the disease to be treated, and the like, but, for example, in case that it is administered orally to an adult (body weight 50 kg) as an analgesic agent, a daily dosage of the compound (I) or (Ia) of the present invention as the active ingredient is about 5 to 1000 mg/day, preferably, about 10 to 600 mg/day, more preferably about 10 to 300 mg/day, particularly preferably about 15 to 150 mg/day, and the dosage can be administered once a day, or 2 or 3 times daily.

[0091] When the compound (I) or (Ia) of the present invention may be used in combination with other drugs, these drugs, separately or simultaneously, may be formulated by mixing with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, and can be administered orally or parenterally. When the drug is prepared separately, the drugs which are prepared separately may be mixed with a diluent or the like before using and then administered, or each of the preparations separately prepared may be administered, simultaneously or separately at an interval, to an identical subject. Kit products used for mixing the separately-prepared preparations with a diluent and the like before using and administering, (for example, an injectable kit including ampoules containing each powdery drug, and a diluent for mixing and solving with 2 or more drugs before using, and the like), kit products used for administering each of the

separately-prepared preparations, simultaneously or separately at an interval, to an identical person, (for example, a tablet kit for administering 2 or more tablets, simultaneously or separately at an interval, wherein the tablet containing each drugs was put into the same or the separate bags and, if necessary, a column wherein the drug administration date is to be indicated was provided on the bag, and the like), or the like are also included in the pharmaceutical composition of the present invention.

[0092] The pharmaceutically acceptable carrier, which may be used for the preparations of the present invention includes a variety of organic or inorganic carrier substances, which have been conventionally employed as formulation materials, for example, an excipient, a lubricant, a binder, and a disintegrator in solid formulations; a solvent, a solubilizer, a suspending agent, an isotonizing agent, a buffering agent, and a soothing agent in liquid formulations; and the like. Also, if required, conventional additives such as a preservative, an antioxidant, a coloring agent, a sweetener, an adsorbent, a wetting agent, and the like can be used.

[0093] Examples of the excipient include lactose, refined sugar, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride, or the like.

[0094] Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, or the like.

[0095] Examples of the binder include crystalline cellulose, refined sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatine, methyl cellulose, sodium carboxymethyl cellulose, or the like.

[0096] Examples of the disintegrator include starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, sodium carboxymethyl starch, L-hydroxypropyl cellulose, or the like.

[0097] Examples of the solvent include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, olive oil, or the like.

[0098] Examples of the solubilizer include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, or the like.

[0099] Examples of the suspending agent include a surface active agent such as stearyltriethanolamine, sodium lauryl sulfate, laurlyaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate, or the like; hydrophilic high molecular weight substances such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, or the like; etc.

[0100] Examples of the isotonizing agent include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, or he like.

[0101] Examples of the buffering agent include a buffering solution of phosphate, acetate, carbonate, citrate or the like.

[0102] Examples of the soothing agent include benzyl alcohol or the like.

[0103] Examples of the preservative include paraoxybenzoic ester, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, or the like.

[0104] Examples of the antioxidant include sulfite, ascorbic acid, α-tocopherol, or the like.

Examples

[0105] The present invention is hereinafter described in more detail by means of the following Examples and Test Examples, but these examples are merely illustrative, and are not intended to limit the present invention.

[0106] The genetic engineering procedures described below were based on the methods described in the textbook (Maniatis, et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or the methods described in the protocols attached to the reagents.

Example 1

N-[4-(Benzhydryloxy)-3-propionylphenyl]-N'-phenylurea

(1) 1-[2-(Benzhydryloxy)-5-nitrophenyl]propan-1-one

[0107] To a solution (20 mL) of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (1.00 g, 5.12 mmole) in DMF was added sodium hydride (60%, 184 mg, 4.61 mmole) under ice-cooling, the mixture was stirred at room temperature for 30 minutes, bromodiphenylmethane (1.52 g, 6.15 mmole) was added to the mixture, and the mixture was stirred at 70°C for 12 hours. Sodium hydride (60%, 184 mg, 4.61 mmole) was further added to the mixture under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. Bromodiphenylmethane (1.52 g, 6.15 mmole) was added to the mixture, and the mixture was stirred at 70°C for 5 hours. The reaction solution was poured into a solution of ice-water containing ammonium chloride, and the mixture was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced

pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain 1.47 g (79.5%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.4 Hz), 2.98 (2H, q, J = 7.4 Hz), 6.39 (1H, s), 6.97 (1 H, d, J = 9.2 Hz), 7.26 to 7.41 (10H, m), 8.15 (1H, dd, J = 9.2, 2.6 Hz), 8.53 (1H, d, J = 2.6 Hz)

(2) 1-[5-Amino-2-(benzhydryloxy)phenyl]propan-1-one

[0108] To a mixed solution of 1-[2-(benzhydryloxy)-5-nitrophenyl]propan-1-one (1.40 g, 0.388 mmole) in ethyl acetate (50 mL) and methanol (50 mL) was added 5% iridium-carbon (300 mg), and the mixture was stirred for 3 hours under hydrogen atmosphere. The insolubles were filtered off, and the filtrate was concentrated, to obtain 450 mg (34.9%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.05 (3H, t, J = 7.4 Hz), 2.95 (2H, q, J = 7.4 Hz), 6.14 (1H, s), 6.60 (1 H, dd, J = 2.6, 8.8 Hz), 6.68 (1H, d, J = 8.8 Hz), 6.95 (1H, d, J = 2.6 Hz), 7.15 to 7.42 (10H, m)

(3) N-[4-(Benzhydryloxy)-3-propionylphenyl]-N'-phenylurea

[0109] To a solution (8 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]propan-1-one (430 mg, 1.30 mmole) in THF was added phenyl isocyanate (0.159 mL, 1.47 mmole) under ice-cooling, and the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate is 3:1) and recrystallized from hexane and ethyl acetate to obtain 372 mg (63.5%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.06 (3H, t, J = 7.4 Hz), 3.00 (2H, q, J = 7.4 Hz), 6.21 (1H, s), 6.82 (1 H, d, J = 9.2 Hz), 7.01 to 7.38 (18H, m), 7.62 (1H, dd, J = 2.6, 8.8 Hz)

Example 2

N-[(4-Benzhydryloxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

[0110] To a solution (4 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]propan-1-one (400 mg, 1.21 mmole) in tetrahydrofuran was added 3,4-dimethoxyphenyl isocyanate (0.216 mL, 1.45 mmole) at 0ºC and the mixture was stirred for 1 hour at 0°C and for 12 hours at room temperature. The solvent was distilled off under reduced pressure and the residue was recrystallized from ethyl acetate, to obtain 610 mg (98.7%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.07 (3H, t, J = 7.2 Hz), 3.01 (2H, q, J = 7.2 Hz), 3.85 (6H, s), 6.24 (1H, s), 6.75 to 7.65 (18H, m)

Example 3

N-[(4-Benzhydryloxy)-3-propionylphenyl]-N'-(3-methoxyphenyl)urea

[0111] To a solution (5 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]propan-1-one (200 mg, 0.603 mmole) and diisopropylethyl amine (0.121 mL, 0.723 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (185 mg, 0.723 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.121 mL, 0.723 mmole) and m-anicidine (0.146 mL, 1.30 mmole), and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain 80 mg (27.7%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.07 (3H, t, J = 7.2 Hz), 3.00 (2H, q, J = 7.2 Hz), 3.77 (3H, s), 6.23 (1H, s), 6.27 to 7.64 (19H, m)

Example 4

N-[(4-Benzhydryloxy)-3-propionylphenyl]-N'-(4-methoxyphenyl)urea

[0112] To a solution (5 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]propan-1-one (200 mg, 0.603 mmole) and diisopropylethyl amine (0.121 mL, 0.723 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (185 mg, 0.723 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.121 mL, 0.723 mmole) and p-anicidine (160 mg, 1.30 mmole), and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted

with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), which was recrystallized from ethyl acetate to obtain 100 mg (34.5%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.06 (3H, t, J = 7.4 Hz), 2.97 (2H, q, J = 7.4 Hz), 3.78 (3H, s), 6.23 (1H, s), 6.68 (1H, s), 6.81 to 7.63 (18H, m)

Example 5

N-[4-(Benzhydryloxy)-3-butylphenyl]-N'-(4-methoxyphenyl)urea

(1) 1-[2-(Benzhydryloxy)-5-nitrophenyl]butan-1-one

[0113] To a solution (30 mL) of 1-(2-hydroxy-5-nitrophenyl)butan-1-one (1.50 g, 7.18 mmole) in DMF was added sodium hydride (60%, 287 mg, 7.18 mmole) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Bromodiphenylmethane (2.13 g, 8.62 mmole) was added to the mixture, and the mixture was stirred for 3 hours at 70°C. The reaction solution was poured into ice-water, and the mixture was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. To the residue was added diisopropylether, to obtain 1.79 g (66.3%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 0.82 (3H, t, J = 7.4 Hz), 1.59 to 1.70 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 6.39 (1H, s), 6.96 (1 H, d, J = 9.2 Hz), 7.35 to 7.41 (10H, m), 8.16 (1H, dd, J = 9.2, 3.0 Hz), 8.50 (1H, d, J = 3.0 Hz)

(2) 1-[5-Amino-2-(benzhydryloxy)phenyl]butan-1-one

[0114] To a solution (100 mL) of 1-[2-(benzhydryloxy)-5-nitrophenyl]butan-1-one (1.74 g, 4.63 mmole) in ethyl acetate was added 5% iridium-carbon (200 mg), and the mixture was stirred for 12 hours under hydrogen atmosphere. The insolubles were filtered off, and the filtrate was concentrated to obtain 1.55 g (96.9%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 0.77 (3H, t, J = 7.4 Hz), 1.50 to 1.64 (2H, m), 2.90 (2H, t, J = 7.4 Hz), 6.13 (1H, s), 6.60 (1 H, dd, J = 3.0, 8.4 Hz), 6.66 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 3.0 Hz), 7.24 to 7.39 (10H, m)

(3) N-[4-(Benzhydryloxy)-3-butylphenyl]-N'-(4-methoxyphenyl)urea

[0115] To a solution (3 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]butan-1-one (300 mg, 0.868 mmole) in THF was added 4-methoxyphenyl isocyanate (0.135 mL, 1.04 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 331 mg (77.2%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 0.76 (3H, t, J = 7.2 Hz), 1.49 to 1.64 (2H, m), 2.92 (2H, t, J = 7.4 Hz), 3.78 (3H, s), 6.22 (1H, s), 6.72 to 7.66 (19H, m)

Example 6

N-[4-(Benzhydryloxy)-3-butylphenyl]-N'-(3-methoxyphenyl)urea

[0116] To a solution (3 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]butan-1-one (300 mg, 0.868 mmole) in THF was added 3-methoxyphenyl isocyanate (0.136 mL, 1.04 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 420 mg (97.9%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 0.76 (3H, t, J = 7.0 Hz), 1.55 to 1.66 (2H, m), 2.95 (2H, t, J = 7.6 Hz), 3.75 (3H, s), 6.22 (1H, s), 6.58 to 7.67 (19H, m)

Example 7

N-[4-(Benzhydryloxy)-3-butylphenyl]-N'-(3,4-dimethoxyphenyl)urea

[0117] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]butan-1-one (300 mg, 0.868 mmole) and diisopropylethyl amine (0.173 mL, 1.04 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (300 mg, 0.868 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.173

mL, 1.04 mmole) and 3.4-dimethoxyaniline (266 mg, 1.74 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 337 mg (74.1%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 0.76 (3H, t, J = 7.2 Hz), 1.54 to 1.65 (2H, m), 2.94 (2H, t, J = 7.6 Hz), 3.85 (6H, s), 6.23 (1H, s), 6.71 to 7.67 (18H, m)

Example 8

N-[3-Acetyl-4-(benzhydryloxy)phenyl]-N'-(4-methoxyphenyl)urea

(1) 1-[2-(benzhydryloxy)-5-nitrophenyl]ethanone

[0118] To a solution (30 mL) of 1-(2-hydroxy-5-nitrophenyl)ethanone (1.50 g, 8.28 mmole) in DMF was added sodium hydride (60%, 331 mg, 8.28 mmole) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Bromodiphenylmethane (2.46 g, 9.94 mmole) was added to the mixture, and the mixture was stirred for 3 hours at 70°C. The reaction solution was poured into ice-water, and the mixture was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. To the residue was added diisopropylether, to obtain 1.87 g (64.9%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 2.63 (3H, s), 6.42 (1H, s), 6.99 (1H, d, J = 9.2 Hz), 7.31 to 7.41 (10H, m), 8.18 (1H, dd, J = 9.2, 3.0 Hz), 8.60 (1H, d, J = 3.0 Hz)

(2) 1-[5-Amino-2-(benzhydryloxy)phenyl]ethanone

[0119] To a solution (200 mL) of 1-(2-hydroxy-5-nitrophenyl)ethanone (1.80 g, 5.18 mmole) in ethyl acetate was added 5% iridium-carbon (180 mg), and the mixture was stirred for 12 hours under hydrogen atmosphere. The insolubles were filtered off, and the filtrate was concentrated, to obtain 1.45 g (88.4%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 2.57 (3H, s), 3.45 (2H, bs), 6.17 (1H, s), 6.64 (1 H, dd, J = 3.0, 8.7 Hz), 6.69 (1H, d, J = 8.7 Hz), 7.03 (1H, d, J = 3.0 Hz), 7.26 to 7.40 (10H, m)

(3) N-[3-Acetyl-4-(benzhydryloxy)phenyl]-N'-(4-methoxyphenyl)urea

[0120] To a solution (3 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]ethanone (300 mg, 0.945 mmole) in THF was added 4-methoxyphenyl isocyanate (0.147 mL, 1.13 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 421 mg (95.7%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 2.61 (3H, s), 3.78 (3H, s), 6.26 (1H, s), 6.77 to 7.75 (19H, m)

Example 9

N-[3-Acetyl-4-(benzhydryloxy)phenyl]-N'-(3-methoxyphenyl)urea

[0121] To a solution (3 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]ethanone (300 mg, 0.945 mmole) in THF was added 3-methoxyphenyl isocyanate (0.147 mL, 1.13 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 350 mg (79.4%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 2.65 (3H, s), 3.75 (3H, s), 6.27 (1H, s), 6.57 to 7.86 (19H, m)

Example 10

N-[3-Acetyl-4-(benzhydryloxy)phenyl]-N'-(3,4-dimethoxyphenyl)urea

[0122] To a solution (3 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]ethanone (300 mg, 0.945 mmole) in THF was added 3,4-dimethoxyphenyl isocyanate (0.168 mL, 1.13 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and

ethyl acetate, to obtain 400 mg (85.3%) of the titled compound as a solid.

H-NMR ($CDCl_3$) δ; 2.63 (3H, s), 3.86 (6H, s), 6.26 (1H, s), 6.68 to 7.81 (18H, m)

Example 11

N-[4-(4-tert-Butylbenzyloxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

(1) 1-[2-(4-tert-Butylbenzyloxy)-5-nitrophenyl]propan-1-one

[0123] A solution of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (500 mg, 2.56 mmole), potassium carbonate (424 mg, 3.07 mmole), 4-tert-butylbenzyl chloride (0.594 mL, 3.07 mmole) and DMF (5 mL) was stirred at 70°C for 12 hours, was poured into water, and was extracted with ethyl acetate. The solvent was distilled off under reduced pressure, to obtain 756 mg (86.5%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.15 (3H, t, J = 7.0 Hz), 1.34 (9H, s), 2.99 (2H, q, J = 7.0 Hz), 5.25 (2H, s), 7.11 (1 H, d, J = 9.2 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.44 (2H, d, J = 8.4 Hz), 8.29 (1H, dd, J = 9.2, 2.8 Hz), 8.56 (1H, d, J = 2.8 Hz)

(2) 1-[5-Amino-2-(4-tert-butylbenzyloxy)phenyl]propan-1-one

[0124] A mixed solution of 1-[2-(4-tert-butylbenzyloxy)-5-nitrophenyl]propan-1-one (700 mg, 2.05 mmole), 5% iridium-carbon (70 mg) and ethyl acetate (7 mL) was stirred for 8 hours at room temperature under hydrogen atmosphere. The insolubles were filtered off, and the solvent was distilled off under reduced pressure, to obtain 583 mg (95.0%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.0 Hz), 1.33 (9H, s), 2.99 (2H, q, J = 7.0 Hz), 5.04 (2H, s), 6.76 (1 H, dd, J = 8.8, 3.0 Hz), 6.86 (1H, d, J = 8.8 Hz), 7.02 (1H, d, J = 3.0 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.40 (2H, d, J = 8.4 Hz)

(3) N-[4-(4-tert-Butylbenzyloxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

[0125] To a solution (2 mL) of 1-[5-amino-2-(4-tert-butylbenzyloxy)phenyl]propan-1-one (200 mg, 0.669 mmole) in THF was added 3,4-dimethoxyphenyl isocyanate (0.119 mL, 0.803 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 293 mg (89.3%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.2 Hz), 1.33 (9H, s), 3.02 (2H, q, J = 7.2 Hz), 3.85 (6H, s), 5.09 (2H, s), 6.75 to 7.83 (12 H, m)

Example 12

N-[4-(4-tert-Butylbenzyloxy)-3-propionylphenyl]-N'-(4-methoxyphenyl)urea

[0126] To a solution (3 mL) of 1-[5-amino-2-(4-tert-butylbenzyloxy)phenyl]propan-1-one (150 mg, 0.501 mmole) in THF was added 4-methoxyphenyl isocyanate (0.0776 mL, 0.599 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 4 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 190 mg (82.3%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.2 Hz), 1.33 (9H, s), 3.00 (2H, q, J = 7.2 Hz), 3.78 (3H, s), 5.07 (2H, s), 6.83 to 7.82 (13 H, m)

Example 13

N-[4-(4-tert-Butylbenzyloxy)-3-propionylphenyl]-N'-(3-methoxyphenyl)urea

[0127] To a solution (3 mL) of 1-[5-amino-2-(4-tert-butylbenzyloxy)phenyl]propan-1-one (150 mg, 0.501 mmole) in THF was added 3-methoxyphenyl isocyanate (0.0785 mL, 0.599 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 193 mg (83.5%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.4 Hz), 1.33 (9H, s), 3.02 (2H, q, J = 7.4 Hz), 3.76 (3H, s), 5.07 (2H, s), 6.60 to 7.82 (13 H, m)

Example 14

N-(3,4-Dimethoxyphenyl)-N'-[4-(4-isopropylbenzyloxy)-3-propionylphenyl]urea

(1) 1-[2-(4-Isopropylbenzyloxy)-5-nitrophenyl]propan-1-one

[0128] A solution of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (500 mg, 2.56 mmole), 4-isopropylbenzyl alcohol (587 mg, 3.84 mmole), 1,1-(azodicarbonyl)dipiperidine (967 mg, 3.84 mmole) and triphenylphosphine (1.01 g, 3.84 mmole) in toluene (5 mL), was stirred for 5 hours at 80°C, to the reaction solution were added 4-isopropylbenzyl alcohol (587 mg, 3.84 mmole), 1,1-(azodicarbonyl)dipiperidine (967 mg, 3.84 mmole) and triphenylphosphine (1.01 g, 3.84 mmole), and the mixture was stirred for 12 hours at 80°C. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain 480 mg (57.3%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.14 (3H, t, J = 7.4 Hz), 1.26 (6H, d, J = 7.0 Hz), 2.91 to 3.04 (3H, m), 5.24 (2H, s), 7.11 (1H, d, J = 9.2 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 8.30 (1H, dd, J = 2.8, 9.2 Hz), 8.56 (1H, d, J = 2.8 Hz)

(2) 1-[5-Amino-2-(4-isopropylbenzyloxy)phenyl]propan-1-one

[0129] A mixture of 1-[2-(4-isopropylbenzyloxy)-5-nitrophenyl]propan-1-one (470 mg, 1.44 mmole), 5% iridium-carbon (50 mg) and ethyl acetate (10 mL) was stirred for 12 hours under hydrogen atmosphere at room temperature, the insolubles were filtered off, and the filtrate was concentrated, to obtain 400 mg (97.8%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.0 Hz), 1.25 (6H, d, J = 7.0 Hz), 2.85 to 3.03 (3H, m), 5.03 (2H, s), 6.75 (1H, dd, J = 2.4, 8.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 7.02 (1H, d, J = 2.4 Hz), 7.23 (2H, dd, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz)

(3) N-(3,4-Dimethoxyphenyl)-N'-[4-(4-isopropylbenzyloxy)-3-propionylphenyl]urea

[0130] To a solution (4 mL) of 1-[5-amino-2-(4-isopropylbenzyloxy)phenyl]propan-1-one (200 mg, 0.701 mmole) in THF was added 3,4-dimethoxyphenyl isocyanate (0.125 mL, 0.842 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 301 mg (89.8%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.4 Hz), 1.25 (6H, d, J = 7.0 Hz), 2.89 to 3.06 (3H, m), 3.86 (6H, s), 5.06 (2H, s), 6.77 to 7.83 (12 H, m)

Example 15

N-(4-Methoxyphenyl)-N'-[4-(4-isopropylbenzyloxy)-3-propionylphenyl]urea

[0131] To a solution (1 mL) of 1-[5-amino-2-(4-isopropylbenzyloxy)phenyl]propan-1-one (100 mg, 0.350 mmole) in THF was added 4-methoxyphenyl isocyanate (0.0544 mL, 0.420 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 123 mg (78.8%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.09 (3H, t, J = 7.5 Hz), 1.26 (6H, d, J = 6.9 Hz), 2.90 to 3.03 (3H, m), 3.78 (3H, s), 5.07 (2H, s), 6.79 to 7.81 (13 H, m)

Example 16

N-(3-Methoxyphenyl)-N'-[4-(4-isopropylbenzyloxy)-3-propionylphenyl]urea

[0132] To a solution (1 mL) of 1-[5-amino-2-(4-isopropylbenzyloxy)phenyl]propan-1-one (100 mg, 0.350 mmole) in THF was added 3-methoxyphenyl isocyanate (0.055 mL, 0.420 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 150 mg (96.2%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.09 (3H, t, J = 7.2 Hz), 1.26 (6H, d, J = 6.9 Hz), 2.90 to 3.03 (3H, m), 3.79 (3H, s), 5.07 (2H, s), 6.79 to 7.81 (13 H, m)

Example 17

N-{4-[(5-Chloropyridin-3-yl)oxy]-3-propionylphenyl}-N'-(3,4-dimethoxyphenyl)urea

(1) 1-{2-[(5-Chloropyridin-3-yl)oxy]-5-nitrophenyl}propan-1-one

[0133] A mixed solution of 1-(2-chloro-5-nitrophenyl)propan-1-one (500 mg, 2.34 mmole), 3-chloro-5-hydroxypyridine (302 mg, 2.34 mmole), potassium carbonate (323 mg, 2.34 mmole) in DMF (5 mL) was stirred for 30 minutes at 70°C, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain 360 mg (50.1%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.22 (3H, t, J = 7.4 Hz), 3.04 (2H, q, J = 7.4 Hz), 6.98 (1H, d, J = 9.2 Hz), 7.44 to 7.46 (1H, m), 8.29 (1H, dd, J = 9.2, 3.0 Hz), 8.30 (1H, d, J = 3.0 Hz), 8.52 (1H, d, J = 2.0 Hz), 8.69 (1H, d, J = 2.6 Hz)

(2) 1-{5-Amino-2-[(5-chloropyridin-3-yl)oxy]phenyl}propan-1-one

[0134] To a mixed solution of 1-{2-[(5-chloropyridin-3-yl)oxy]-5-nitrophenyl}propan-1-one (350 mg, 0.978 mmole) in methanol (14 mL) and water (3.5 mL) was added sodium hydrosulfite (579 mg, 3.33 mmole), and the mixture was stirred for 40 minutes at 80°C. Sodium hydrosulfite (1.16 g, 6.66 mmole) was added to the mixture, the mixture was stirred for 80 minutes at 80°C, and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to obtain 108 mg (40.0%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 6.8 Hz), 2.86 (2H, q, J = 6.8 Hz), 6.83 to 6.84 (2H, m), 7.07 to 7.09 (1H, m), 7.15 to 7.17 (1H, m), 8.24 (1H, d, J = 2.6 Hz), 8.27 (1H, d, J = 2.6 Hz)

(3) N-{4-[(5-Chloropyridin-3-yl)oxy]-3-propionylphenyl}-N'-(3,4-dimethoxyphenyl)urea

[0135] To a solution (1 mL) of 1-{5-amino-2-[(5-chloropyridin-3-yl)oxy]phenyl}propan-1-one (108 mg, 0.391 mmole) in THF was added 3,4-dimethoxyphenyl isocyanate (0.698 mL, 0.469 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 130 mg (73.0%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.0 Hz), 2.92 (2H, q, J = 7.0 Hz), 3.88 (6H, s), 6.76 to 7.27 (7H, m), 7.57 (1H, d, J = 2.6 Hz), 7.83 (1H, dd, J = 2.6, 8.6 Hz), 8.26 (1H, d, J = 2.6 Hz), 8.33 (1H, d, J = 2.2 Hz)

Example 18

N-{4-[(5-Chloropyridin-3-yl)oxy]-3-propionylphenyl}-N'-(4-methoxyphenyl)urea

[0136] To a solution (1 mL) of 1-(5-amino-2-[(5-chloropyridin-3-yl)oxy]phenyl}propan-1-one (110 mg, 0.398 mmole) in THF was added 4-methoxyphenyl isocyanate (0.619 mL, 0.478 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 4 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain 114 mg (67.5%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.4 Hz), 2.91 (2H, q, J = 7.4 Hz), 3.82 (3H, s), 6.85 to 7.28 (8H, m), 7.55 (1H, d, J = 3.0 Hz), 7.82 (1H, dd, J = 3.0, 8.8 Hz), 8.26 (1H, d, J = 2.6 Hz), 8.33 (1H, d, J = 1.8 Hz)

Example 19

N-{4-[(5-Chloropyridin-3-yl)oxy]-3-propionylphenyl}-N'-(3-methoxyphenyl)urea

[0137] To a solution (1 mL) of 2-{5-amino-2-[(5-chloropyridin-3-yl)oxy]phenyl}propan-1-one (110 mg, 0.398 mmole) in THF was added 3-methoxyphenyl isocyanate (0.626 mL, 0.478 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 4 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 88.0 mg (52.1%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.2 Hz), 2.90 (2H, q, J = 7.2 Hz), 3.73 (3H, s), 6.58 to 7.77 (10H, m), 8.22 (1H, d, J = 2.6 Hz), 8.33 (1H, d, J = 1.8 Hz)

Example 20

2-Benzhydryloxy-N-(tert-butyl)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzamide

(1) 2-Benzhydryloxy-N-(tert-butyl)-5-nitrobenzamide

[0138] To a solution (10 mL) of N-(tert-butyl)-2-hydroxy-5-nitrobenzamide (500 mg, 2.10 mmole) in DMF was added sodium hydride (60%, 168 mg, 4.20 mmole) under ice-cooling, and the mixture was stirred for 30 minutes at room temperature. Bromodiphenylmethane (623 mg, 2.52 mmole) was added thereto, and the mixture was stirred for 3.5 hours at 70°C. Bromodiphenylmethane (623 mg, 2.52 mmole) was further added to the mixture, and the mixture was stirred at 70°C for 12 hours. The mixture was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 9:1), to obtain 530 mg (62.4%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.19 (9H, s), 6.45 (1H, s), 6.93 (1H, d, J = 9.2 Hz), 7.35 to 7.45 (10H, m), 7.61 (1H, s), 8.08 to 8.15 (1H, m), 9.06 to 9.08 (1H, m)

(2) 5-Amino-2-benzhydryloxy-N-(tert-butyl)benzamide

[0139] A mixed solution of 2-benzhydryloxy-N-(tert-butyl)-5-nitrobenzamide (800 mg, 1.98 mmole), 5% iridium-carbon (100 mg) and ethyl acetate (20 mL) was stirred for 12 hours under hydrogen atmosphere. The insolubles were filtered off, and the filtrate was concentrated, to obtain 667 mg (90.0%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.16 (9H, s), 6.18 (1H, s), 6.52 to 6.64 (2H, m), 7.29 to 7.37 (10H, m), 7.50 (1H, d, J = 3.0 Hz), 7.91 (1H, bs)

(3) 2-Benzhydryloxy-N-(tert-butyl)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzamide

[0140] To a solution (5 mL) of 5-amino-2-benzhydryloxy-N-(tert-butyl)benzamide (200 mg, 0.534 mmole) and diisopropylethyl amine (0.107 mL, 0.640 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (164 mg, 0.640 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. This solution was added to a solution of diisopropylethyl amine (0.107 mL, 0.640 mmole) and p-anicidine (142 mg, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 121 mg (43.4%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.16 (9H, s), 3.77 (3H, s), 6.26 (1H, s), 6.54 (1H, s), 6.76 to 7.73 (18H, m), 7.88 (1H, s)

Example 21

2-Benzhydryloxy-N-(tert-butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide

[0141] To a solution (3 mL) of 5-amino-2-benzhydryloxy-N-(tert-butyl)benzamide (300 mg, 0.801 mmole) in THF was added 3,4-dimethoxyphenyl isocyanate (0.143 mL, 0.961 mmole) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. This compound was recrystallized from hexane and ethyl acetate.

^{1}H-NMR ($CDCl_3$) δ; 1.16 (9H, s), 3.82 (3H, s), 3.83 (3H, s), 6.27 (1H, s), 6.75 to 7.92 (19H, m)

Example 22

Methyl 5-(anilinocarbonylamino)-2-benzhydryloxybenzoate

(1) Methyl 2-benzhydryloxy-5-nitrobenzoate

[0142] To a solution (200 mL) of methyl 2-hydroxy-5-nitrobenzoate (10.0 g, 50.7 mmole) in DMF was added sodium hydride (60%, 1.93 g, 48.2 mmole) under ice-cooling, the mixture was stirred for 30 minutes at room temperature, and bromodiphenylmethane (15.0 g, 60.9 mmole) was added thereto. The mixture was stirred at 70°C for 12 hours, was

poured into ice-water containing ammonium chloride (2.71 g, 50.7 mmole), and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate and hexane, to obtain 11.3 g (61.4%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 3.99 (3H, s), 6.41 (1H, s), 7.02 (1H, d, J = 9.6 Hz), 7.24 to 7.55 (10H, m), 8.18 (1H, dd, J = 9.6, 3.0 Hz), 8.72 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-benzhydryloxybenzoate

[0143] A mixed solution of methyl 2-benzhydryloxy-5-nitrobenzoate (4.00 g, 11.0 mmole), 5% iridium-carbon (400 mg) and ethyl acetate (80 mL) was stirred for 4 hours under hydrogen atmosphere. The insolubles were removed, and the filtrate was concentrated, to obtain 3.60 g (98.1%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 3.45 (2H, bs), 3.84 (3H, s), 6.13 (1H, s), 6.61 (1H, dd, J = 2.4, 8.8 Hz), 6.69 (1H, d, J = 8.8 Hz), 7.13 (1H, d, J = 2.4 Hz), 7.19 to 7.51 (10H, m)

(3) Methyl 5-(anilinocarbonylamino)-2-benzhydryloxybenzoate

[0144] A mixed solution of methyl 5-amino-2-benzhydryloxybenzoate (3.60 g, 10.8 mmole), phenyl isocyanate (1.30 mL, 12.2 mmole) and THF (70 mL) was stirred at room temperature for 2 hours, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate and diisopropylether, to obtain 2.77 g (56.6%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 6.16 (1H, s), 6.76 (1H, d, J = 9.0 Hz), 6.99 to 7.49 (18H, m), 7.60 (1H, d, J = 2.6 Hz)

Example 23

Methyl 2-(benzhydryloxy)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0145] A mixed solution of methyl 5-amino-2-benzhydryloxybenzoate (200 mg, 0.600 mmole), 4-methoxyphenyl isocyanate (0.0876 mL, 0.678 mmole) and THF (2 mL) was stirred at room temperature for 2 hours, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate and hexane, to obtain 200 mg (68.9%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 3.76 (3H, s), 3.86 (3H, s), 6.20 (1H, s), 6.55 (1H, s), 6.63 (1H, s), 6.80 to 7.60 (17H, m)

Example 24

Methyl 2-(benzhydryloxy)-5-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0146] To a solution (13 mL) of methyl 5-amino-2-benzhydryloxybenzoate (500 mg, 1.50 mmole) and diisopropylethyl amine (0.308 mL, 1.80 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (461 mg, 1.80 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution was added diisopropylethyl amine (0.308 mL, 1.80 mmole) and m-anicidine (0.202 mL, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), which was recrystallized from ether and ethyl acetate, to obtain 408 mg (56.4%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.71 (3H, s), 3.86 (3H, s), 6.18 (1H, s), 6.56 to 7.61 (19H, m)

Example 25

Methyl 2-(benzhydryloxy)-5-({[(4-ethoxyphenyl)amino]carbonyl}amino)benzoate

[0147] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and p-fenetidine (0.232 mL, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The

solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), which was recrystallized from hexane and ethyl acetate, to obtain 400 mg (80.5%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.40 (3H, t, J = 7.0 Hz), 3.87 (3H, s), 3.99 (2H, q, J = 7.0 Hz), 6.21 (1H, s), 6.41 (1H, s), 6.51 (1H, s), 6.81 to 7.60 (17H, m)

Example 26

Methyl 2-(benzhydryloxy)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0148] To a solution (13 mL) of methyl 5-amino-2-benzhydryloxybenzoate (500 mg, 1.50 mmole) and diisopropylethyl amine (0.308 mL, 1.80 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (461 mg, 1.80 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.308 mL, 1.80 mmole) and 3,4-dimethoxyaniline (275 mg, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane: ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 352 mg (45.8%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.81 (6H, s), 3.86 (3H, s), 6.20 (1H, s), 6.65 to 7.61 (18H, m)

Example 27

Methyl 2-(benzhydryloxy)-5-({[(3-ethoxyphenyl)amino]carbonyl}amino)benzoate

[0149] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and m-fenetidine (0.239 mL, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 265 mg (53.4%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.35 (3H, t, J = 7.0 Hz), 3.86 (3H, s), 3.95 (2H, q, J = 7.0 Hz), 6.20 (1H, s), 6.58 to 7.62 (19H, m)

Example 28

Methyl 2-(benzhydryloxy)-5-({[(3-nitrophenyl)amino]carbonyl}amino)benzoate

[0150] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and m-nitroaniline (0.239 mL, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 310 mg (64.3%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 6.12 (1H, s), 6.77 (1H, d, J = 9.2 Hz), 7.16 to 7.98 (18H, m)

Example 29

Methyl 2-(benzhydryloxy)-5-[(morpholin-4-ylcarbonyl)amino]benzoate

[0151] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl

amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and morpholine (0.105 mL, 1.20 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (ethyl acetate), which was recrystallized from hexane and ethyl acetate, to obtain 268 mg (60.0%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.42 (4H, t, J = 4.4 Hz), 3.71 (4H, t, J = 4.4 Hz), 3.88 (3H, s), 6.24 (1H, s), 6.27 (1H, s), 6.84 (1H, d, J = 9.2 Hz), 7.19 to 7.52 (11H, m), 7.65 (1H, d, J = 3.0 Hz)

Example 30

Methyl 2-(benzhydryloxy)-5-{[(1, 3-benzodioxol-5-ylamino)carbonyl]amino}benzoate

[0152] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and 3,4-methylenedioxyaniline (165 mg, 1.20 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 354 mg (71.2%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.82 (3H, s), 5.79 (2H, s), 6.15 (1H, s), 6.48 to 7.56 (18H, m)

Example 31

Methyl 2-(benzhydryloxy)-5-({[(3-acetylphenyl)amino]carbonyl}amino)benzoate

[0153] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and 3'-aminoacetophenone (243 mg, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (ethyl acetate), which was recrystallized from ethyl acetate, to obtain 199 mg (40.2%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 2.59 (3H, s), 3.90 (3H, s), 6.26 (1H, s), 6.85 (1H, d, J = 8.8 Hz), 7.19 to 7.95 (16H, m), 8.07 (1H, s), 8.30 (1H, s)

Example 32

Methyl 2-(benzhydryloxy)-5-{[(pyridin-4-ylamino)carbonyl]amino}benzoate

[0154] To a solution (10 mL) of methyl 5-amino-2-benzhydryloxybenzoate (333 mg, 1.00 mmole) and diisopropylethyl amine (0.205 mL, 1.20 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (307 mg, 1.20 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.205 mL, 1.20 mmole) and 4-aminopyridine (169 mg, 1.80 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (ethyl acetate:THF = 4:1), which was recrystallized from ethyl acetate and hexane, to obtain 106 mg (23.4%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.88 (3H, s), 6.21 (1H, s), 6.84 (1H, d, J = 9.2 Hz), 7.22 to 7.50 (14H, m), 7.64 (1H, bs), 7.70 (1H, d, J = 2.8 Hz), 8.30 (2H, d, J = 6.0 Hz)

Example 33

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(tert-butyl)benzamide

(1) 5-(Anilinocarbonylamino)-2-benzhydryloxy benzoic acid

[0155] A mixed solution of methyl 5-(anilinocarbonylamino)-2-benzhydryloxybenzoate (1.60 g, 3.54 mmole), 1N aqueous solution of sodium hydroxide (7 mL) and methanol (70 mL) was heated to reflux for 12 hours, was poured into water, and was washed with ethyl acetate. The aqueous layer was neutralized with 1N hydrochloric acid, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. To the residue was added diisopropylether, and the mixture was filtered to obtain 939 mg (60.6%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 6.39 (1H, s), 6.88 to 7.02 (2H, m), 7.22 to 7.46 (14H, m), 7.72 (1H, d, J = 2.6 Hz), 7.93 (1H, dd, J = 2.6, 9.0 Hz), 8.01 (1H, s), 8.26 (1H, s)

(2) 5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(tert-butyl)benzamide

[0156] A solution (3 mL) of 5-(anilinocarbonylamino)-2-benzhydryloxy benzoic acid (300 mg, 0.684 mmole), tert-butyl amine (0.144 mL, 1.37 mmole), 1-hydroxy-1H-benzotriazole (157 mg, 1.03 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (164 mg, 0.855 mmole) in DMF was stirred at 0°C for 1 hour and at room temperature for 12 hours, and was poured into water. The mixture was extracted with ethyl acetate, the extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), which was recrystallized from hexane and ethyl acetate, to obtain 274 mg (81.1%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.18 (9H, s), 6.27 (1H, s), 6.77 (1 H, d, J = 8.8 Hz), 7.02 (1H, d, J = 7.0 Hz), 7.21 to 7.34 (14H, m), 7.46 (1H, s), 7.65 to 7.75 (3H, m), 7.89 (1H, s)

Example 34

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(tert-pentyl)benzamide

[0157] A solution (2 mL) of 5-(anilinocarbonylamino)-2-benzhydryloxy benzoic acid (200 mg, 0.456 mmole), tert-pentyl amine (0.107 mL, 0.912 mmole), 1-hydroxy-1H-benzotriazole (105 mg, 0.687 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (109 mg, 0.570 mmole) in DMF was stirred at 0°C for 1 hour and at room temperature for 12 hours, and was poured into water. The mixture was extracted with ethyl acetate, the extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), which was recrystallized from hexane and ethyl acetate, to obtain 174 mg (75.3%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 0.65 (3H, t, J = 7.6 Hz), 1.10 (6H, s), 1.55 (2H, q, J = 7.6 Hz), 6.29 (1H, s), 6.79 (1H, d, J = 9.2 Hz), 7.02 (1 H, t, J = 7.4 Hz), 7.26 to 7.79 (19H, m)

Example 35

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(1-methyl-1-phenylethyl)benzamide

[0158] A solution (2 mL) of 5-(anilinocarbonylamino)-2-benzhydryloxy benzoic acid (200 mg, 0.456 mmole), cumylamine (123 mg, 0.912 mmole), 1-hydroxy-1H-benzotriazole (105 mg, 0.687 mmole) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (109 mg, 0.570 mmole) in DMF was stirred at 0°C for 1 hour and at room temperature for 12 hours, and was poured into water. The mixture was extracted with ethyl acetate, the extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), which was recrystallized from hexane and ethyl acetate, to obtain 95.0 mg (37.5%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 1.38 (6H, s), 6.33 (1H, s), 6.81 (1H, d, J = 8.8 Hz), 6.96 (1H, t, J = 6.8 Hz), 7.09 to 7.63 (23H, m), 8.44 (1H, s)

Example 36

tert-Butyl 2-(benzhydryloxy)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

(1) tert-Butyl 2-benzhydryloxy-5-nitrobenzoate

[0159] To a solution (20 mL) of tert-butyl 2-hydroxy-5-nitrobenzoate (1.17 g, 4.90 mmole) in DMF was added sodium hydride (60%, 235 mg, 5.87 mmole) under ice-cooling, and the mixture was stirred for 30 minutes at room temperature. Bromodiphenylmethane (1.45 g, 5.88 mmole) was added to the mixture, and the mixture was stirred at 70°C for 12 hours, and poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain 610 mg (30.6%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.57 (9H, s), 6.38 (1H, s), 6.94 (1H, d, J = 9.2 Hz), 7.26 to 7.49 (10H, m), 8.13 (1H, dd, J = 9.2, 2.8 Hz), 8.51 (1H, d, J = 2.8 Hz)

(2) tert-Butyl5-amino-2-benzhydryloxy benzoate

[0160] A mixed solution of tert-butyl 2-benzhydryloxy-5-nitrobenzoate (600 mg, 1.48 mmole), 5% iridium-carbon (60 mg) and ethyl acetate (10 mL) was stirred for 12 hours under hydrogen atmosphere. The insolubles were removed, and the filtrate was concentrated, to obtain 400 mg (72.1%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.49 (9H, s), 6.13 (1H, s), 6.53 (1H, dd, J = 3.4, 8.4 Hz), 6.62 (1H, d, J = 8.4 Hz), 6.95 (1H, d, J = 3.4 Hz), 7.15 to 7.47 (10H, m)

(3) tert-Butyl 2-(benzhydryloxy)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0161] A mixed solution of methyl 5-amino-2-benzhydryloxybenzoate (200 mg, 0.533 mmole), 4-methoxyphenyl isocyanate (0.0829 mL, 0.639 mmole) and THF (2 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and was extracted with ethyl acetate. The residue was recrystallized from ethyl acetate and hexane to obtain 139 mg (49.6%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.60 (9H, s), 3.79 (3H, s), 6.22 (1H, s), 6.33 (1H, s), 6.38 (1H, s), 6.77 to 7.46 (17H, m)

Example 37

Isopropyl 2-(benzhydryloxy)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

(1) Isopropyl 2-benzhydryloxy-5-nitrobenzoate

[0162] To a solution (110 mL) of isopropyl 2-hydroxy-5-nitrobenzoate (5.64 g, 25.0 mmole) in DMF was added sodium hydride (60%, 1.10 g, 27.5 mmole) under ice-cooling, the mixture was stirred for 30 minutes at room temperature. Bromodiphenylmethane (7.41 g, 30.0 mmole) was added to the mixture, the mixture was stirred at 70°C for 12 hours, was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from diisopropylether, to obtain 3.28 g (33.5%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.35 (6H, d, J = 6.2 Hz), 5.25 to 5.37 (1H, m), 6.41 (1H, s), 6.99 (1H, d, J = 9.6 Hz), 7.24 to 7.52 (10H, m), 8.15 (1H, dd, J = 9.6, 3.0 Hz), 8.64 (1H, d, J = 3.0 Hz)

(2) Isopropyl 5-amino-2-benzhydryloxy benzoate

[0163] A mixed solution of isopropyl 2-benzhydryloxy-5-nitrobenzoate (3.23 g, 8.25 mmole), 5% iridium-carbon (300 mg) and ethyl acetate (100 mL) was stirred for 12 hours under hydrogen atmosphere. The insolubles were filtered off, and the filtrate was concentrated, to obtain 2.80 g (94.0%) of the titled compound as oil.

^{1}H-NMR ($CDCl_3$) δ; 1.27 (6H, d, J = 6.2 Hz), 5.17 to 5.29 (1H, m), 6.16 (1H, s), 6.57 (1H, dd, J = 2.6, 8.8 Hz), 6.66 (1H, d, J = 8.8 Hz), 7.08 (1H, d, J = 2.6 Hz), 7.19 to 7.49 (10H, m)

(3) Isopropyl 2-(benzhydryloxy)-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0164] A mixed solution of isopropyl 5-amino-2-benzhydryloxy benzoate (300 mg, 0.830 mmole), 4-methoxyphenyl

isocyanate (0.129 mL, 0.996 mmole) and THF (2 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and was extracted with ethyl acetate. The residue was recrystallized from ethyl acetate and hexane to obtain 376 mg (88.9%) of the titled compound.

^{1}H-NMR ($CDCl_3$) δ; 1.28 (6H, d, J = 6.2 Hz), 3.75 (3H, s), 5.17 - 5.30 (1H, m), 6.22 (1H, s), 6.58 (1H, s), 6.68 (1H, s), 6.80 to 7.52 (17H, m)

Example 38

Methyl 2-(benzhydryloxy)-5-({[(4-hydroxy-3-methoxybenzyl)amino]carbonyl}amino)benzoate

[0165] To a solution (5 mL) of methyl 5-amino-2-benzhydryloxybenzoate (200 mg, 0.600 mmole) and diisopropylethyl amine (0.123 mL, 0.720 mmole) in acetonitrile was added N,N-disuccinimidyl carbamate (184 mg, 0.720 mmole) at 0°C, and the mixture was stirred for 1 hour at 0°C. To this solution were added diisopropylethyl amine (0.247 mL, 1.44 mmole) and 4-hydroxy-3-methoxybenzyl amine hydrochloride (136 mg, 0.720 mmole), and the mixture was stirred for 12 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), which was recrystallized from hexane and ethyl acetate, to obtain 187 mg (68.2%) of the titled compound as a solid.

^{1}H-NMR ($CDCl_3$) δ; 3.82 (3H, s), 3.86 (3H, s), 4.28 (2H, d, J = 5.4 Hz), 4.96 (1H, t, J = 5.4 Hz), 5.59 (1H, s), 6.22 (1H, s), 6.32 (1H, s), 6.70 to 7.51 (15H, m), 7.61 (1H, d, J = 3.0 Hz)

Example 39

N-[4-(2-Chlorobenzyloxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

(1) 1-[2-(2-Chlorobenzyloxy)-5-nitrophenyl]propan-1-one

[0166] A solution of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (500 mg, 2.56 mmol), potassium carbonate (424 mg, 3.07 mmol), 2-chlorobenzylchloride (0.388 mL, 3.07 mmol) and DMF (5 mL) was stirred at 70°C for 12 hours, was poured into water, and was extracted with ethyl acetate. The solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 630 mg (76.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.14 (3H, t, J = 7.4 Hz), 2.97 (2H, q, J = 7.4 Hz), 5.37 (2H, s), 7.11 (1 H, d, J = 9.2 Hz), 7.26 to 7.49 (4H, m), 8.33 (1H, dd, J = 9.2, 3.0 Hz), 8.57 (1H, d, J = 3.0 Hz)

(2) 1-[5-Amino-2-(2-chlorobenzyloxy)phenyl]propan-1-one

[0167] To a mixed solution (30 mL) of 1-[2-(2-chlorobenzyloxy)-5-nitrophenyl]propan-1-one (610 mg, 1.91 mmol) in methanol and water (8 mL) was added sodium hydrosulfite (4.53 g, 26.0 mmol) for 4 hours at 80°C. The mixture was stirred for 1 hour at 80°C and the solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 220 mg (39.8%)

^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.2 Hz), 2.99 (2H, q, J = 7.2 Hz), 3.53 (2H, bs), 5.17 (2H, s), 6.77 (1H, dd, J = 3.0, 8.6 Hz), 6.84 (1H, d, J = 8.6 Hz), 7.01 (1H, d, J = 3.0 Hz), 7.26 to 7.53 (4 H, m)

(3) N-[4-(2-Chlorobenzyloxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

[0168] To a solution (1 mL) of 1-[5-amino-2-(2-chlorobenzyloxy)phenyl]propan-1-one (100 mg, 0.345 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.0616 mL, 0.414 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 138 mg (85.2%)

^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 6.8 Hz), 3.00 (2H, q, J = 6.8 Hz), 3.85 (6H, s), 5.21 (2H, s), 6.77 to 7.82 (12 H, m)

[0169] The following compounds were obtained in the same manner as Example 39.

Example 40

N-[4-(2-Chlorobenzyloxy)-3-propionylphenyl]-N'-(3-methoxyphenyl)urea

[0170] ^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.4 Hz), 3.01 (2H, q, J = 7.4Hz), 3.76 (3H, s), 5.20 (2H, s), 6.59 to 7.83 (13 H, m)

Example 41

N-[4-(1,1'-Biphenyl-4-ylmethoxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

(1) 1-(2-(1,1'-Biphenyl-4-ylmethoxy)-5-nitrophenyl]propan-1-one

[0171] ^{1}H-NMR ($CDCl_3$) δ; 1.16 (3H, t, J = 7.0 Hz), 3.01 (2H, q, J = 7.0 Hz), 5.32 (2H, s), 7.14 (1 H, d, J = 9.2 Hz), 7.37 to 7.68 (9H, m), 8.32 (1H, dd, J = 9.2, 2.8 Hz), 8.58 (1H, d, J = 2.8Hz)
IR (KBr) cm^{-1}; 1676, 1607, 1584, 1510, 1480, 1420, 1345, 1277, 982, 766, 750

(2) 1-[5-Amino-2-(1,1'-biphenyl-4-ylmethoxy)phenyl]propan-1-one

[0172] ^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.4 Hz), 3.00 (2H, q, J = 7.4Hz), 5.11 (2H, s), 6.77 (1H, dd, J = 3.0, 8.4 Hz), 6.88 (1H, d, J = 8.4 Hz), 7.03 (1H, d, J = 3.0 Hz), 7.32 to 7.64 (9 H, m)

(3) N-[4-(1,1'-Biphenyl-4-ylmethoxy)-3-propionylphenyl]-N'-(3,4-dimethoxyphenyl)urea

[0173] ^{1}H-NMR ($CDCl_3$) δ; 1.12 (3H, t, J = 7.4 Hz), 3.03 (2H, q, J = 7.4 Hz), 3.85 (6H, s), 5.15 (2H, s), 6.78 to 7.85 (17 H, m)

Example 42

N-[4-(1,1'-Biphenyl-4-ylmethoxy)-3-propionylphenyl]-N'-(3-methoxyphenyl)urea

[0174] ^{1}H-NMR ($CDCl_3$) δ; 1.13 (3H, t, J = 7.4 Hz), 3.04 (2H, q, J = 7.4 Hz), 3.78 (3H, s), 5.15 (2H, s), 6.61 to 7.85 (18 H, m)

Example 43

N-[4-(1,1'-Biphenyl-4-ylmethoxy)-3-propionylphenyl]-N'-(4-methoxyphenyl)urea

[0175] ^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.0 Hz), 3.01 (2H, q, J = 7.0 Hz), 3.77 (3H, s), 5.13 (2H, s), 6.83 to 7.83 (18 H, m)

Example 44

N-(3,4-Dimethoxyphenyl)-N'-[4-(4-ethylbenzyloxy)-3-propionylphenyl]urea

(1) 1-[2-(4-Ethylbenzyloxy)-5-nitrophenyl]propan-1-one

[0176] A solution (5 mL) of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (500 mg, 2.56 mmol), 4-ethylbenzyl alcohol (0.508 mL, 3.84 mmol), 1,1-(azodicarbonyl)dipiperidine (967 mg, 3.84 mmol) and triphenylphosphine (1.01 g, 3.84 mmol) in toluene was stirred at 80°C for 3 hours, to the reaction solution were added 4-ethylbenzyl alcohol (0.508 mL, 3.84 mmol), 1,1-(azodicarbonyl)dipiperidine (967 mg, 3.84 mmol), triphenylphosphine (1.01 g, 3.84 mmol) and toluene (5 mL), and the mixture was stirred at 80°C for 3 hours. To the reaction solution were further added 4-ethylbenzyl alcohol (0.508 mL, 3.84 mmol), 1,1-(azodicarbonyl)dipiperidine (967 mg, 3.84 mmol), triphenylphosphine (1.01 g, 3.84 mmol) and toluene (5 mL), and the mixture was stirred for 12 hours at 80°C. The reaction solution was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain the titled compound as oil. 770 mg (96.0%)
^{1}H-NMR ($CDCl_3$) δ; 1.13 (3H, t, J = 7.4 Hz), 1.24 (3H, t, J = 7.8 Hz), 2.65 (2H, q, J = 7.8 Hz), 2.97 (2H, q, J = 7.4

Hz), 5.24 (2H, s), 7.11 (1H, d, J = 9.2 Hz), 7.20 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz), 8.29 (1H, dd, J = 3.0, 9.2 Hz), 8.56 (1H, d, J = 3.0 Hz)

(2) 1-[5-Amino-2-(4-ethylbenzyloxy)phenyl]propan-1-one

[0177] To a solution (80 mL) of 1-[2-(4-ethylbenzyloxy)-5-nitrophenyl]propan-1-one (750 mg, 2.39 mmol) in ethyl acetate was added 5% iridium carbon (75 mg), and the mixture was stirred for 12 hours under hydrogen atmosphere. The insolubles were filtered off, and the filtrate was concentrated, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain titled compound as oil. 530 mg (78.3%)

^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.5 Hz), 1.25 (3H, t, J = 7.8 Hz), 2.66 (2H, q, J = 7.8 Hz), 2.97 (2H, q, J = 7.5 Hz), 3.50 (2H, bs), 5.03 (2H, s), 6.76 (1H, dd, J = 3.0, 9.0 Hz), 6.86 (1H, d, J = 9.0 Hz), 7.02 (1H, d, J = 3.0 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.1 Hz)

(3) N-(3,4-Dimethoxyphenyl)-N'-[4-(4-ethylbenzyloxy)-3-propionylphenyl]urea

[0178] To a solution (2 mL) of 1-[5-amino-2-(4-ethylbenzyloxy)phenyl]propan-1-one (200 mg, 0.706 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.126 mL, 0.847 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 295 mg (90.2%)

^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.4 Hz), 1.24 (3H, t, J = 7.6 Hz), 2.66 (2H, q, J = 7.6 Hz), 3.00 (2H, q, J = 7.4 Hz), 3.84 (6H, s), 5.06 (2H, s), 6.76 to 7.84 (12 H, m)

[0179] The following compounds were obtained in the same manner as Example 44.

Example 45

N-[4-(4-Ethylbenzyloxy)-3-propionylphenyl]-N'-(3-methoxyphenyl)urea

[0180] ^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.4 Hz), 1.24 (3H, t, J = 7.2 Hz), 2.66 (2H, q, J = 7.2 Hz), 3.01 (2H, q, J = 7.4 Hz), 3.76 (3H, s), 5.05 (2H, s), 6.58 to 7.84 (13 H, m)

Example 46

N-[4-(4-Ethylbenzyloxy)-3-propionylphenyl]-N'-(4-methoxyphenyl)urea

[0181] ^{1}H-NMR ($CDCl_3$) δ; 1.09 (3H, t, J = 7.4 Hz), 1.25 (3H, t, J = 7.6 Hz), 2.66 (2H, q, J = 7.6 Hz), 2.98 (2H, q, J = 7.6 Hz), 3.78 (3H, s), 5.05 (2H, s), 6.828 to 7.82 (13 H, m)

Example 47

N-(3,4-Dimethoxyphenyl)-N'-[4-(2,4-dimethylbenzyloxy)-3-propionylphenyl]urea

(1) 1-[2-(2,4-Dimethylbenzyloxy)-5-nitrophenyl]propan-1-one

[0182] ^{1}H-NMR ($CDCl_3$) δ; 1.09 (3H, t, J = 7.4 Hz), 2.34 (6H, s), 2.90 (2H, q, J = 7.4 Hz), 5.21 (2H, s), 6.99 to 7.26 (4H, m), 8.32 (1H, dd, J = 2.6, 9.2 Hz), 8.55 (1H, d, J = 2.6 Hz)

(2) 1-[5-Amino-2-(2,4-dimethylbenzyloxy)phenyl]propan-1-one

[0183] ^{1}H-NMR ($CDCl_3$) δ; 1.06 (3H, t, J = 7.2 Hz), 2.33 (6H, s), 2.91 (2H, q, J = 7.2 Hz), 3.50 (2H, bs), 5.00 (2H, s), 6.78 (1H, dd, J = 2.8, 8.8 Hz), 6.87 (1H, d, J = 8.8 Hz), 7.00 to 7.26 (4H, m)

(3) N-(3,4-Dimethoxyphenyl)-N'-[4-(2,4-dimethylbenzyloxy)-3-propionylphenyl]urea

[0184] ^{1}H-NMR ($CDCl_3$) δ; 1.06 (3H, t, J = 7.4 Hz), 2.32 (6H, s), 2.93 (2H, q, J = 7.4 Hz), 3.85 (6H, s), 5.05 (2H, s), 6.77 to 7.86 (11 H, m)

Example 48

N-[4-(2,4-Dimethylbenzyloxy)-3-propionylphenyl]-N'-(3-methoxyphenyl)urea

[0185] ^{1}H-NMR ($CDCl_3$) δ; 1.07 (3H, t, J = 7.4 Hz), 2.32 (6H, s), 2.95 (2H, q, J = 7.4 Hz), 3.77 (3H, s), 5.05 (2H, s), 6.59 to 7.87 (12 H, m)

Example 49

N-[4-(2,4-Dimethylbenzyloxy)-3-propionylphenyl]-N'-(4-methoxyphenyl)urea

[0186] ^{1}H-NMR ($CDCl_3$) δ; 1.05 (3H, t, J = 7.4 Hz), 2.32 (6H, s), 2.94 (2H, q, J = 7.4 Hz), 3.79 (3H, s), 5.04 (2H, s), 6.76 to 7.84 (12 H, m)

Example 50

N-(3,4-Dimethoxyphenyl)-N'-[4-(4-methylbenzyloxy)-3-propionylphenyl]urea

(1) 1-[2-(4-Methylbenzyloxy)-5-nitrophenyl]propan-1-one

[0187] ^{1}H-NMR ($CDCl_3$) δ; 1.13 (3H, t, J = 7.0 Hz), 2.38 (3H, s), 2.96 (2H, q, J = 7.0 Hz), 5.23 (2H, s), 7.10 (1 H, d, J = 9.2 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 8.29 (1H, dd, J = 9.2, 3.0 Hz), 8.56 (1H, d, J = 3.0 Hz)

(2) 1-[5-Amino-2-(4-methylbenzyloxy)phenyl]propan-1-one

[0188] ^{1}H-NMR ($CDCl_3$) δ; 1.09 (3H, t, J = 7.2 Hz), 2.36 (3H, s) , 2.97 (2H, q, J = 7.2 Hz), 3.50 (2H, bs), 5.02 (2H, s), 6.75 (1H, dd, J = 2.2, 8.4 Hz), 6.85 (1H, d, J = 8.4 Hz), 7.01 (1H, d, J = 2.2 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz)

(3) N-(3,4-Dimethoxyphenyl)-N'-[4-(4-methylbenzyloxy)-3-propionylphenyl]urea

[0189] ^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.2 Hz), 2.37 (3H, s), 3.00 (2H, q, J = 7.2 Hz), 3.85 (6H, s), 5.06 (2H, s), 6.76 to 7.85 (12 H, m)

Example 51

N-(3-Methoxyphenyl)-N'-[4-(4-methylbenzyloxy)-3-propionylphenyl]urea

[0190] ^{1}H-NMR ($CDCl_3$) δ; 1.11 (3H, t, J = 7.2 Hz), 2.37 (3H, s), 3.00 (2H, q, J = 7.2 Hz), 3.76 (3H, s), 5.04 (2H, s), 6.58 to 7.86 (13 H, m)

Example 52

N-(4-Methoxyphenyl)-N'-[4-(4-methylbenzyloxy)-3-propionylphenyllurea

[0191] ^{1}H-NMR ($CDCl_3$) δ; 1.08 (3H, t, J = 7.4 Hz), 2.36 (3H, s), 2.97 (2H, q, J = 7.4 Hz), 3.78 (3H, s), 5.05 (2H, s), 6.82 to 7.81 (13 H, m)

Example 53

N-(3,4-Dimethoxyphenyl)-N'-(4-neopentyl-3-propionylphenyl)urea

(1) 1-[2-Neopentyloxy-5-nitrophenyl]propan-1-one

[0192] To a solution (10 mL) of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (500 mg, 2.56 mmol) in DMF was added sodium hydride (60%, 123 mg, 3.07 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Neopentyl iodide (0.407 mL, 3.07 mmol) was added to the mixture, and the mixture was stirred for 2 hours at 120°C. Neopentyl iodide (0.407 mL, 3.07 mmol) was further added to the mixture, and the mixture was stirred at 120°C

for 12 hours, and was poured into water. This solution was extracted with ethyl acetate, and the extracted solution was washed with water and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 9:1), to obtain the titled compound as a solid. 200 mg (29.5%)

^{1}H-NMR ($CDCl_3$) δ; 1.10 (9H, s), 1.21 (3H, t, J = 7.4 Hz), 3.04 (2H, q, J = 7.4 Hz), 3.81 (2H, s), 7.04 (1 H, d, J = 9.0 Hz), 8.31 (1H, dd, J = 9.0, 2.8 Hz), 8.54 (1H, d, J = 2.8Hz)

(2) 1-[5-Amino-2-neopentyloxyphenyl]propan-1-one

[0193] 1-[2-Neopentyloxy-5-nitrophenyl]propan-1-one (190 mg, 0.716 mmol) and 5% iridium carbon (20 mg) were added thereto, and the mixture was stirred for 12 hours under hydrogen atmosphere at room temperature. The insolubles were filtered off, and the filtrate was concentrated, to obtain the titled compound as oil. 153 mg (90.5%)

^{1}H-NMR ($CDCl_3$) δ; 1.05 (9H, s), 1.17 (3H, t, J = 7.4 Hz), 3.04 (2H, q, J = 7.4 Hz), 3.48 (3H, bs), 3.61 (2H, s), 6.78 (2 H, d, J = 1.8 Hz), 7.02 (1H, t, J = 1.8 Hz)

(3) N-(3,4-Dimethoxyphenyl)-N'-(4-neopentyl-3-propionylphenyl)urea

[0194] To a solution (3 mL) of 1-[5-amino-2-neopentyloxyphenyl]propan-1-one (143 mg, 0.608 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.108 mL, 0.729 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 213 mg (84.5%)

^{1}H-NMR ($CDCl_3$) δ; 1.07 (9H, s), 1.18 (3H, t, J = 7.4 Hz), 3.08 (2H, q, J = 7.6 Hz), 3.67 (2H, s), 3.87 (6H, s), 6.76 to 6.94 (5H, m), 7.06 (1H, d, J = 1.8 Hz), 7.36 (1H, d, J = 3.0 Hz), 7.77 to 7.83 (1H, m)

[0195] The following compounds were obtained in the same manner as Example 53.

Example 54

N-(3,4-Dimethoxyphenyl)-N'-(4-isobutoxy-3-propionylphenyl)urea

(1) 1-[2-Isobutoxy-5-nitrophenyl]propan-1-one

[0196] ^{1}H-NMR ($CDCl_3$) δ; 1.09 (6H, d, J = 7.0 Hz), 1.20 (3H, t, J = 7.4 Hz), 2.14 to 2.28 (1H, m), 3.01 (2H, q, J = 7.4 Hz), 3.94 (2H, d, J = 6.6 Hz), 7.03 (1 H, d, J = 9.2 Hz), 8.31 (1H, dd, J = 9.2, 2.8 Hz), 8.56 (1H, d, J = 2.8Hz)

(2) 1-[5-Amino-2-isobutoxyphenyl]propan-1-one

[0197] ^{1}H-NMR ($CDCl_3$) δ; 1. 03 (6H, d, J = 7.0 Hz), 1.16 (3H, t, J = 7.4 Hz), 2.04 to 2.17 (1H, m), 3.01 (2H, q, J = 7.4 Hz), 3.50 (2H, bs), 3.73 (2H, d, J = 6.4 Hz), 6.77 (2 H, d, J = 1.8 Hz), 7.03 (1H, t, J = 1.8 Hz)

(3) N-(3,4-Dimethoxyphenyl)-N'-(4-isobutoxy-3-propionylphenyl)urea

[0198] ^{1}H-NMR ($CDCl_3$) δ; 1.05 (6H, d, J = 6.6 Hz), 1.17 (3H, t, J = 7.4 Hz), 2.05 to 2.20 (1H, m), 3.05 (2H, q, J = 7.4 Hz), 3.78 (2H, d, J = 6.2 Hz), 3.86 (6H, s), 6.73 to 7.09 (6H, m), 7.37 (1H, d, J = 2.8 Hz), 7.82 (1H, dd, J = 2.8, 9.2 Hz)

Example 55

N-(4-Cyclohexylmethoxy-3-propionylphenyl)-N'-(3,4-dimethoxyphenyl)urea

(1) 1-(2-Cyclohexylmethoxy-5-nitrophenyl)propan-1-one

[0199] ^{1}H-NMR ($CDCl_3$) δ; 1.08 to 1.90 (14H, m), 3.01 (2H, q, J = 7.2 Hz), 3.96 (3H, d, J = 5.8 Hz), 7.03 (1 H, d, J = 9.0 Hz), 8.30 (1H, dd, J = 9.0, 2.6 Hz), 8.55 (1H, d, J = 2.6Hz)

(2) 1-(5-Amino-2-cyclohexylmethoxyphenyl)propan-1-one

[0200] ^{1}H-NMR ($CDCl_3$) δ; 1.03 to 1.88 (14H, m), 3.00 (2H, q, J = 7.2 Hz), 3.47 (2H, bs), 3.75 (2H, d, J = 5.6 Hz), 6.77 (2 H, d, J = 2.0 Hz), 7.02 (1H, t, J = 2.0 Hz)

(3) N-(4-Cyclohexylmethoxy-3-propionylphenyl)-N'-(3,4-dimethoxyphenyl)urea

[0201] ^{1}H-NMR ($CDCl_3$) δ; 1.04 to 1.88 (14H, m), 3.04 (2H, q, J = 7.4 Hz), 3.81 (2H, d, J = 5.8 Hz), 3.86 (6H, s), 6.78 to 7.08 (6H, m), 7.35 (1H, d, J = 2.8 Hz), 7.80 (1H, dd, J = 2.8, 9.2 Hz)

Example 56

N-(4-Cyclohexylmethoxy-3-propionylphenyl)-N'-(3-methoxyphenyl)urea

[0202] ^{1}H-NMR ($CDCl_3$) δ; 1.10 to 1.88 (14H, m), 3.05 (2H, q, J = 7.4 Hz), 3.78 (3H, s), 3.81 (2H, d, J = 6.0 Hz), 6.60 to 7.26 (7H, m), 7.38 (1H, d, J = 3.0 Hz), 7.80 (1H, dd, J = 3.0, 9.0 Hz)

Example 57

N-(4-Cyclohexylmethoxy-3-propionylphenyl)-N'-(4-methoxyphenyl)urea)

[0203] ^{1}H-NMR ($CDCl_3$) δ; 1.12 to 1.87 (14H, m), 3.02 (2H, q, J = 7.4 Hz), 3.78 to 3.81 (5H, m), 6.82 to 7.26 (7H, m), 7.33 (1H, d, J = 3.0 Hz), 7.79 (1H, dd, J = 3.0, 8.8 Hz)

Reference Example 1

1-(2-Hydroxy-5-nitrophenyl)-2-methylpropan-1-one

(1) 4-Nitrophenyl 2-methylpropanate

[0204] To a solution (400 mL) of 4-nitrophenol (20.0 g, 144 mmol) and triethyl amine (24.0 mL, 173 mmol) in tetrahydrofuran was added dropwise isobutyl chloride (18.1 mL, 173 mmol) under ice-cooling, the mixture was stirred for 1 hour under ice-cooling, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 30.0 g (99.7%)

^{1}H-NMR ($CDCl_3$) δ; 1.34 (6H, d, J = 6.8 Hz), 2.78 - 2.92 (1H, m), 3.81 (3H, s), 7.27 (2 H, d, J = 9.2 Hz), 8.27 (2H, d, J = 9.2 H)

(2) 1-(2-Hydroxy-5-nitrophenyl)-2-methylpropan-1-one

[0205] To a suspension (70 mL) of aluminium chloride (34.1 g, 256 mmol) in nitrobenzene was added dropwise a solution of 4-nitrophenyl 2-methylpropanate (15.0 g, 71.7 mmol) in nitrobenzene (70 mL). The mixture was stirred for 2 hours at room temperature, for 2 hours at 100°C and for 3 hours at 110 to 130°C, and the reaction solution was poured into ice-water. 1N hydrochloric acid (400 mL) was added to the mixture, and the mixture was extracted with ethyl acetate. The extracted solution was washed with water, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil.

3.40 g (22.7%)

^{1}H-NMR ($CDCl_3$) δ; 1.31 (6H, d, J = 6.6 Hz), 3.62 to 3.76 (1H, m), 7.11 (1 H, d, J = 9.2 Hz), 8.35 (1H, dd, J = 9.2, 2.6 Hz), 8.77 (1H, d, J = 2.6 Hz)

Example 58

N-(4-Benzhydryloxy-3-isobutyrylphenyl)-N'-(3,4-dimethoxyphenyl)urea

(1) 1-[2-(Benzhydryloxy)-5-nitrophenyl]-2-methylpropan-1-one

[0206] A solution (10 mL) of 1-(2-hydroxy-5-nitrophenyl)-2-methylpropan-1-one (1.00 g, 4.78 mmol) in DMF was added to a solution of sodium hydride (60%, 191 mg, 4.78 mmol) under ice-cooling, and the mixture was stirred at room temperature for 0.5 hour. Bromodiphenylmethane (1.42 g, 5.74 mmol) was added to the mixture, and the mixture was stirred for 12 hours at 70°C. The reaction solution was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl ac-

etate = 30:1), to obtain the titled compound as oil.

1.00 g (55.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.10 (6H, d, J = 7.0 Hz), 3.37 to 3.44 (1H, m), 6.37 (1H, s), 6.95 (1 H, d, J = 9.2 Hz), 7.26 to 7.38 (10H, m), 8.15 (1H, dd, J = 9.2, 2.4 Hz), 8.35 (1H, d, J = 2.4 Hz)

(2) 1-[5-Amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one

[0207] 1-[2-(Benzhydryloxy)-5-nitrophenyl]-2-methylpropan-1-one (950 mg, 2.53 mmol) and 5% iridium carbon (100 mg) were added thereto, and the mixture was stirred for 12 hours under hydrogen atmosphere at room temperature. The insolubles were filtered off, and the filtrate was concentrated, to obtain the titled compound as a solid.

630 mg (72.1%)

^{1}H-NMR ($CDCl_3$) δ; 1.03 (6H, d, J = 7.0 Hz), 3.43 to 3.57 (3H, m), 6.10 (1H, s), 6.58 (1H, dd, J = 3.4, 8.8 Hz), 6.65 (1 H, d, J = 8.8 Hz), 6.79 (1H, d, J = 3.4 Hz), 7.26 to 7.39 (10H, m)

(3) N-(4-Benzhydryloxy-3-isobutylphenyl)-N'-(3,4-dimethoxyphenyl)urea

[0208] To a solution (4 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.103 mL, 0.695 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 278 mg (91.4%)

^{1}H-NMR ($CDCl_3$) δ; 1.06 (6H, d, J = 6.6 Hz), 3.51 to 3.58 (1H, m), 3.85 (6H, s), 6.21 (1H, s), 6.64 to 7.36 (17H, m), 7.55 (1H, dd, J = 3.0, 8.8 Hz)

Example 59

N-(4-Benzhydryloxy-3-isobutylphenyl)-N'-(3-methoxyphenyl)urea

[0209] To a solution (4 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in THF was added 3-methoxyphenyl isocyanate (0.0911 mL, 0.695 mmol) under ice-cooling, the mixture was stirred for 1 hour at 0°C, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 272 mg (89.5%)

^{1}H-NMR ($CDCl_3$) δ; 1.05 (6H, d, J = 7.0 Hz), 3.51 to 3.62 (1H, m), 3.78 (3H, s), 3.75 (3H, s), 6.19 (1H, s), 6.58 to 7.35 (18H, m), 7.53 (1H, dd, J = 2.6, 9.0 Hz)

Example 60

N-(4-Benzhydryloxy-3-isobutylphenyl)-N'-(4-methoxyphenyl)urea

[0210] To a solution (4 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in THF was added 4-methoxyphenyl isocyanate (0.0900 mL, 0.695 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 254 mg (88.8%)

^{1}H-NMR ($CDCl_3$) δ; 1.04 (6H, d, J = 6.6 Hz), 3.49 to 3.56 (1H, m), 3.79 (3H, s), 6.20 (1H, s), 6.51 to 7.36 (18H, m), 7.54 (1H, dd, J = 3.0, 8.8 Hz)

Example 61

N-(3,4-Dimethoxyphenyl)-N'-[4-(3,3-diphenylpropoxy)-3-propionylphenyl]urea

(1) 1-[2-(3,3-Diphenylpropoxy)-5-nitrophenyl]propan-1-one

[0211] A solution (5 mL) of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (500 mg, 2.56 mmol), 3,3-diphenylpropanol (765 mg, 3.84 mmol), 1,1-(azodicarbonyl)dipiperidine (969 mg, 3.84 mmol) and triphenylphosphine (1.01 g, 3.84 mmol) in toluene was stirred for 4 hours at 80°C, and to the reaction solution were added 3,3-diphenylpropanol (765 mg, 3.84 mmol), 1,1-(azodicarbonyl)dipiperidine (969 mg, 3.84 mmol), triphenylphosphine (1.01 g, 3.84 mmol) and toluene (5 mL). The mixture was stirred for 4 hours at 80°C. To the reaction solution were further added 3,3-diphenylpropanol (765 mg, 3.84 mmol), 1,1-(azodicarbonyl)dipiperidine (967 mg, 3.84 mmol), triphenylphosphine (1.01 g, 3.84 mmol) and toluene (5 mL), and the mixture was stirred for 12 hours at 80°C. The reaction solution was poured into water, and

was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 600 mg (60.2%)

^{1}H-NMR ($CDCl_3$) δ; 1.23 (3H, t, J = 7.2 Hz), 2.58 - 2.69 (2H, m), 3.04 (2H, q, J = 7.2 Hz), 4.07 to 4.25 (3H, m), 6.87 (1 H, d, J = 9.0 Hz), 7.15 to 7.36 (10H, m), 8.24 (1H, dd, J = 9.0, 2.8 Hz), 8.55 (1H, d, J = 2.8Hz)

(2) 1-[5-Amino-2-(3,3-diphenylpropoxy)-phenyl]propan-1-one

[0212] 1-[2-(3,3-Diphenylpropoxy)-5-nitrophenyl]propan-1-one (590 mg, 1.51 mmol) and 5% iridium carbon (100 mg) were added thereto, and the mixture was stirred for 12 hours under hydrogen atmosphere at room temperature. The insolubles were filtered off, and the filtrate was concentrated, to obtain the titled compound as a solid. 530 mg (97.4%)

^{1}H-NMR ($CDCl_3$) δ; 1.18 (3H, t, J = 7.4 Hz), 2.49 - 2.60 (2H, m), 3.04 (2H, q, J = 7.42 Hz), 3.47 (2H, bs), 3.90 (2 H, t, J = 6.2 Hz), 4.22 (1H, t, J = 6.2 Hz), 6.62 (1H, d, J = 8.4 Hz), 6.72 (1 H, dd, J = 8.4, 2.8 Hz), 7.02 (1H, d, J = 2.8 Hz), 7.16 to 7.34 (10H, m)

(3) N-(3,4-Dimethoxyphenyl)-N'-[4-(3,3-diphenylpropoxy)-3-propionylphenyl]urea

[0213] To a solution (2 mL) of 1-[5-amino-2-(3,3-diphenylpropoxy)-phenyl]propan-1-one (200 mg, 0.556 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.0994 mL, 0.668 mmol) under ice-cooling, the mixture was stirred for 1 hour at 0°C, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 285 mg (95.3%)

^{1}H-NMR ($CDCl_3$) δ; 1.23 (3H, t, J = 7.4 Hz), 2.52 - 2.62 (2H, m), 3.07 (2H, q, J = 7.4 Hz), 3.85 (6H, s), 3.97 (2H, t, J = 6.6 Hz), 4.21 (1H, t, J = 8.0 Hz), 6.73 to 7.37 (17H, m), 7.73 to 7.78 (1H, m)

Example 62

N-[4-(3,3-Diphenylpropoxy)-3-propionylphenyl]-N-(3-methoxyphenyl)urea

[0214] To a solution (2 mL) of 1-[5-amino-2-(3,3-diphenylpropoxy)-phenyl]propan-1-one (150 mg, 0.417 mmol) in THF was added 3-methoxyphenyl isocyanate (0.0648 mL, 0.500 mmol) under ice-cooling, the mixture was stirred for 1 hour at 0°C, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 180 mg (84.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.18 (3H, t, J = 7.2 Hz), 2.52 - 2.62 (2H, m), 3.05 (2H, q, J = 7.2 Hz), 3.79 (3H, s), 3.96 (2H, t, J = 6.2 Hz), 4.21 (1H, t, J = 8.0 Hz), 6.57 to 7.34 (18H, m), 7.71 to 7.77 (1H, m)

Example 63

N-[4-(3,3-diphenylpropoxy)-3-propionylphenyl]-N-(4-methoxyphenyl)urea

[0215] To a solution THF (2 mL) of 1-[5-amino-2-(3,3-diphenylpropoxy)-phenyl]propan-1-one (150 mg, 0.417 mmol) in was added 4-methoxyphenyl isocyanate (0.0655 mL, 0.500 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 205 mg (96.7%)

^{1}H-NMR ($CDCl_3$) δ; 1.21 (3H, t, J = 7.4 Hz), 2.51 - 2.62 (2H, m), 3.08 (2H, q, J = 7.2 Hz), 3.76 (3H, s), 3.96 (2H, t, J = 6.6 Hz), 4.20 (1H, t, J = 7.6 Hz), 6.59 to 7.39 (18H, m), 7.73 to 7.79 (1H, m)

Example 64

Methyl [4-(3,4-dimethoxyphenylaminocarbonylamino)-2-propionylphenoxy]acetate

(1) Methyl (4-nitro-2-propionylphenoxy)acetate

[0216] To a solution (20 mL) of 1-(2-hydroxy-5-nitrophenyl)propan-1-one (1.00 g, 5.12 mmol) in DMF was added sodium hydride (60%, 205 mg, 5.12 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. Methyl bromoacetate (0.582 mL, 6.14 mmol) was added to the mixture under ice-cooling, and the mixture was stirred at room temperature for 6 hours, and was poured into water. The mixture was extracted with ethyl acetate, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 1.29 g (94.2%)

^{1}H-NMR ($CDCl_3$) δ; 1.21 (3H, t, J = 7.4 Hz), 3.11 (2H, q, J = 7.4 Hz), 3.85 (3H, s), 4.86 (2H, s), 6.92 (1H, d, J = 9.2 Hz), 7.25 (2 H, d, J = 9.2 Hz), 8.27 (2H, d, J = 9.2, 3.0 H), 8.60 (1H, d, J = 3.0 Hz)

(2) Methyl (4-amino-2-propionylphenoxy)acetate

[0217] Methyl (4-nitro-2-propionylphenoxy)acetate (1.26 g, 4.72 mmol), 5% iridium carbon (200 mg) and ethyl acetate (40 mL) stirred for 24 hours under hydrogen atmosphere. The solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 1.10 g (98.2%)

^{1}H-NMR ($CDCl_3$) δ; 1.17 (3H, t, J = 7.4 Hz), 3.08 (2H, q, J = 7.4 Hz), 3.80 (3H, s), 4.64 (2H, s), 6.69 (1H, d, J = 6.8 Hz), 6.76 (1H, dd, J = 3.0, 6.8 Hz), 7.02 (1 H, d, J = 3.0 Hz)

(3) Methyl [4-(3,4-dimethoxyphenylaminocarbonylamino)-2-propionylphenoxy]acetate

[0218] To a solution (40 mL) of methyl (4-amino-2-propionylphenoxy) acetate (1.10 g, 4.64 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.827 mL, 5.56 mmol) under ice-cooling, the mixture was stirred for 2 hours under ice-cooling, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 1.58 g (81.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.18 (3H, t, J = 7.2 Hz), 3.15 (2H, q, J = 7.2 Hz), 3.82 (3H, s), 3.85 (6H, s), 4.68 (2H, s), 6.74 to 7.38 (7H, m), 7.84 to 7.88 (1H, m)

Example 65

[4-(3,4-Dimethoxyphenylaminocarbonylamino)-2-propionylphenoxy]acetic acid

[0219] To a mixed solution (50 mL) of methyl [4-(3,4-dimethoxyphenylaminocarbonylamino)-2-propionylphenoxy] acetate (1.40 g, 3.36 mmol) in THF and methanol (20 mL) was added 1N aqueous solution of sodium hydroxide (10 mL), and the mixture was stirred at room temperature for 4 hours. The reaction solution was poured into water, acidified with 1N hydrochloric acid, and was extracted with ethyl acetate. The solvent was distilled off under reduced pressure, and the residue was purified with ethyl acetate. 1.30 g (96.3%)

^{1}H-NMR ($CDCl_3$) δ; 1.16 (3H, t, J = 7.2 Hz), 3.14 (2H, q, J = 7.2 Hz), 3.4 (3H, s), 3.88 (3H, s), 4.67 (2H, s), 6.69 to 6.86 (3H, m), 7.35 (1H, d, J = 2.2 Hz), 7.49 (1H, d, J = 2.2 Hz), 7.83 (1H, dd, J = 3.0, 8.8 Hz), 7.97 (1H, s), 8.18 (1H, s)

Example 66

N-Benzhydryl-2-[4-(3,4-dimethoxyphenylaminocarbonylamino)-2-propionylphenoxy]acetamide

[0220] A solution (2 mL) of [4-(3,4-dimethoxyphenylaminocarbonylamino)-2-propionylphenoxy]acetic acid (200 mg, 0.497 mmol), 1-hydroxy-1H-benzotriazole (115 mg, 0.749 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (119 mg, 0.621 mmol) in DMF was stirred at 0°C for 1 hour. Aminodiphenylmethane (0.171 mL, 0.994 mmol) was added to the mixture, the mixture was stirred at room temperature for 12 hours, and was poured into water. The mixture was extracted with ethyl acetate, and the extracted solution was washed with water and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (tetrahydrofuran), to obtain the titled compound as a solid. This was recrystallized from ethyl acetate. 31.0 mg (11.0%)

^{1}H-NMR ($CDCl_3$) δ; 1.10 (3H, t, J = 7.4 Hz), 2.90 (2H, q, J = 7.4 Hz), 3.89 (6H, s), 4.61 (2H, s), 6.35 (1H, d, J = 9.2 Hz), 6.59 to 7.33 (17H, m), 7.89 (1H, d, J = 2.6 Hz), 8.74 (1H, d, J = 9.2 Hz)

IR (KBr) cm^{-1}; 3295, 1682, 1549, 1495, 1209, 1028, 700

Example 67

N-(4-Benzhydryloxy-3-isobutyrylphenyl)-N'-(3,4-dihydro-1, 4-benzodioxim-6-yl)urea

[0221] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in acetonitrile were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and N,N'-disuccinimidyl carbonate (178 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred for 1 hour under ice-cooling. To the reaction solution were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and 3,4-ethylenedioxyaniline (105 mg, 0.695 mmol) under ice-cooling, the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours. The reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, and was

dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as a solid.

113 mg (37.4%)

^{1}H-NMR ($CDCl_3$) δ; 1.04 (6H, d, J = 6.6 Hz), 3.46 to 3.60 (1H, m), 4.23 (4H, s), 6.20 (1H, s), 6.51 (1H, bs), 6.70 to 7.58 (17H, m)

Example 68

N-(4-Benzhydryloxy-3-isobutylphenyl)-N'-(3,4-diethoxyphenyl)urea

(1) 1,2-Ethoxy-4-nitrobenzene

[0222] A mixture of 4-nitrocatechol (5.00 g, 32.2 mmol), potassium carbonate (10.7 g, 77.4 mmol), iodoethane (6.19 mL, 77.4 mmol) and DMF (100 mL) was stirred at 70°C for 12 hours, and the reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 6.50 g (95.6%)

^{1}H-NMR ($CDCl_3$) δ; 1.47 to 1.57 (6H, m), 4.12 to 4.25 (4H, m), 6.89 (1H, d, J = 9.2 Hz), 7.73 (1H, d, J = 2.6 Hz), 7.88 (1H, dd, J = 2.6, 9.2 Hz)

(2) 3,4-Diethoxy aniline

[0223] A solution of 1, 2-ethoxy-4-nitrobenzene (6.30 g, 29.9 mmol), 10% palladium carbon (600 mg) and ethanol (300 mL) was stirred under hydrogen atmosphere for 6 hours. The insolubles were filtered off, and the filtrate was concentrated, to obtain the titled compound as oil. 5.02 g (92.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.34 to 1.46 (6H, m), 3.94 to 4.08 (4H, m), 6.21 (1H, d, J = 2.8, 8.4Hz), 6.30 (1H, d, J = 2.6 Hz), 6.73 (1H, d, J = 8.4 Hz)

(3) N-(4-Benzhydryloxy-3-isobutylphenyl)-N'-(3,4-diethoxyphenyl)urea

[0224] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in acetonitrile were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and N,N'-disuccinimidyl carbonate (178 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. To the reaction solution were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and 3,4-diethoxyaniline (126 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours. The reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as a solid.

236 mg (73.8%)

^{1}H-NMR ($CDCl_3$) δ; 1.04 (6H, d, J = 6.4 Hz), 1.39 to 1.46 (6H, m), 3.51 to 3.57 (1H, m), 3.99 to 4.11 (4H, m), 6.21 (1H, s), 6.64 to 7.58 (18H, m)

Example 69

N-[4-(Benzhydryloxy)-3-isobutylphenyl]-N'-(1H-benzoimidazol-6-yl)urea

(1) 1H-benzoimidazol-5-amine

[0225] A mixture of 5-nitrobenzoimidazol (2.00 g, 12.3 mmol) and 10% palladium carbon (200 mg) in ethanol (100 mL) and THF (100 mL) was stirred under hydrogen atmosphere at room temperature for 4 hours. The insolubles were filtered off, the filtrate was evaporated under reduced pressure, to obtain the titled compound as a solid. 1.50 g (92.0%)

^{1}H-NMR ($CDCl_3$) δ; 6.67 (1H, dd, J = 2.2, 9.2 Hz), 6.86 (1H, d, J = 2.2 Hz), 7.43 (1H, d, J = 9.2 Hz), 7.84 (1H, s)

(2) N-[4-(Benzhydryloxy)-3-isobutylphenyl]-N'-(1H-benzoimidazol-6-yl)urea

[0226] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (190 mg, 0.550 mmol) in acetonitrile were added diisopropylethyl amine (0.110 mL, 0.660 mmol) and N,N'-disuccinimidyl carbonate (169 mg, 0.660 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. To the reaction solution were

added diisopropylethyl amine (0.110 mL, 0.660 mmol) and 1H-benzoimidazol-5-amine (87.8 mg, 0.6605 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours. The reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (ethyl acetate:methanol = 10:1). The fractions containing the titled compound were collected, which was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 102 mg (36.7%)

^{1}H-NMR ($CDCl_3$) δ; 0.96 (6H, d, J = 7.0 Hz), 3.39 to 3.46 (1H, m), 6.07 (1H, s), 6.63 to 6.77 (2H, m), 7.18 to 7.46 (15H, m), 8.16 (2H, bs)

Example 70

N-{4-[Bis(4-fluorophenyl)methoxy]-3-isobutylphenyl}-N'-(3,4-dimethoxyphenyl)urea

(1) 1-{2-[Bis(4-fluorophenyl)methoxy]-5-nitrophenyl}-2-methylpropan-1-one

[0227] A mixture of 1-(2-hydroxy-5-nitrophenyl)-2-methylpropan-1-one (500 mg, 2.39 mmol), 4,4'-difluorobenzhydrol (1.05 g, 4.78 mmol), 40% solution of diethyl azodicarbonate in toluene (2.08 g, 4.78 mmol) and a solution of triphenylphosphine (1.25 g, 4.78 mmol) in DMF (5 mL) was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 9:1), to obtain the titled compound as oil. 600 mg (61.0%)

^{1}H-NMR ($CDCl_3$) δ; 1.10 (6H, d, J = 7.0 Hz), 3.29 to 3.36 (1H, m), 6.35 (1H, s), 6.91 (1 H, d, J = 9.0 Hz), 7.26 to 7.36 (8H, m), 8.15 (1H, dd, J = 9.0, 2.8 Hz), 8.33 (1H, d, J = 2.8 Hz)

(2) 1-{5-Amino-2-[bis(4-fluorophenyl)methoxy]phenyl}-2-methylpropan-1-one

[0228] 1-{2-[Bis(4-fluorophenyl)methoxy]-5-nitrophenyl}-2-methylpropan-1-one (600 mg, 1.46 mmol) and 5% iridium carbon (100 mg) were added thereto, and the mixture was stirred for 12 hours under hydrogen atmosphere at room temperature. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (1:1), to obtain the titled compound as a solid. 200 mg (35.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.03 (6H, d, J = 7.0 Hz), 3.36 to 3.43 (1H, m), 3.48 (2H, bs), 6.06 (1H, s), 6.59 (2 H, d, J = 1.8 Hz), 6.77 (1H, t, J = 1.8 Hz), 6.98 to 7.08 (4H, m), 7.26 to 7.33 (4H, m)

(3) N-{4-[Bis(4-fluorophenyl)methoxy]-3-isobutylphenyl}-N'-(3,4-dimethoxyphenyl)urea

[0229] To a solution (4 mL) of 1-{5-amino-2-[bis(4-fluorophenyl)methoxy]phenyl}-2-methylpropan-1-one (190 mg, 0.498 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.0889 mL, 0.598 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 261 mg (93.5%)

^{1}H-NMR ($CDCl_3$) δ; 1.04 (6H, d, J = 7.0 Hz), 3.62 to 3.49 (1H, m), 3.86 (3H, s), 3.87 (3H, s), 6.17 (1H, s), 6.56 (1H, s), 6.73 to 7.59 (15H, m)

Example 71

N-[4-(Benzhydryloxy)-3-isobutylphenyl]-N'-(3,4-dihydro-2H-1, 5-benzodioxepin-7-yl)urea

[0230] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in acetonitrile were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and N,N'-disuccinimidyl carbonate (178 mg, 0.695 mmol) under ice-cooling and the mixture was stirred under ice-cooling for 1 hour. To the reaction solution was added diisopropylethyl amine (0.116 mL, 0.695 mmol) and 3,4-dihydro-2H-1, 5-benzooxepin-7-amine (115 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 2 hours. The reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as a solid. 147 mg (47.3%)

^{1}H-NMR ($CDCl_3$) δ; 1.04 (6H, d, J = 7.0 Hz), 2.14 to 2.19 (2H, m), 3.50 to 3.57 (1H, m), 4.13 to 4.21 (4H, m),

6.21 (1H, s), 6.65 (1H, bs), 6.79 to 7.57 (17H, m)

Example 72

N-[4-(Benzhydryloxy)-3-isobutylphenyl]-N'-(1,3-benzodioxol-5-yl)urea

[0231] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in acetonitrile were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and N,N'-disuccinimidyl carbonate (178 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. To the reaction solution were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and 3,4-(methylenedioxy)aniline (95.3 mg, 0.695 mmol) under ice-cooling; and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 1 hour. The reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 135 mg (45.9%)

^{1}H-NMR ($CDCl_3$) δ; 1.02 (6H, d, J = 7.0 Hz), 3.46 to 3.60 (1H, m), 5.86 (3H, s), 6.17 (1H, s), 6.57 to 7.53 (18H, m)

Example 73

N-{5-[({[4-(Benzhydryloxy)-3-isobutyrylphenyl]amino}carbonyl)amino]-2-methoxyphenyl}methane sulfonamide

(1) N-(2-Methoxy-5-nitrophenyl)methane sulfonamide

[0232] To a solution (15 mL) of 2-amino-4-nitroanisol (5.00 g, 29.7 mmol) in pyridine was added dropwise methane sulfonylchloride (3.45 mL, 44.6 mmol), and the mixture was stirred at room temperature for 2 hours and was poured into water, to obtain the titled compound as a solid. 7.00 g (96.4%)

^{1}H-NMR ($CDCl_3$) δ; 3.09 (3H, s), 4.03 (3H, s), 6.98 to 7.02 (2H, m), 8.07 (1H, dd, J = 8.8, 2.6 Hz), 8.41 (1H, d, J = 2.6 Hz)

(2) N-(5-Amino-2-methoxyphenyl)methane sulfonamide

[0233] To a mixed solution of N-(2-methoxy-5-nitrophenyl)methane sulfonamide (6.90 g, 28.0 mmol) in THF (150 mL) and ethanol (150 mL) was added 10% palladium carbon (690 mg), and the mixture was stirred under hydrogen atmosphere for 5 hours. The insolubles were filtered off, and the filtrate was concentrated, to obtain the titled compound as a solid. 6.00 g (99.0%)

^{1}H-NMR ($CDCl_3$) δ; 2.96 (3H, s), 3.52 (2H, bs), 3.80 (3H, s), 6.44 (1H, dd, J = 1.8, 5.6 Hz), 6.73 (1H, d, J = 5.6 Hz), 6.79 (1H, bs), 6.95 (1H, d, J = 1.8 Hz)

(3) N-{5-[({[4-(Benzhydryloxy)-3-isobutyrylphenyl]amino}carbonyl)amino]-2-methoxyphenyl}methane sulfonamide

[0234] To a solution (6 mL) of 1-[5-amino-2-(benzhydryloxy)phenyl]-2-methylpropan-1-one (200 mg, 0.579 mmol) in acetonitrile were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and N,N'-disuccinimidyl carbonate (178 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour. To the reaction solution were added diisopropylethyl amine (0.116 mL, 0.695 mmol) and N-(5-amino-2-methoxyphenyl)methane sulfonamide(150 mg, 0.695 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours. The reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. The product was recrystallized from hexane and ethyl acetate. 80.0 mg (23.5%)

^{1}H-NMR ($CDCl_3$) δ; 1.05 (6H, d, J = 7.0 Hz), 2.97 (3H, s), 3.46 to 3.56 (1H, m), 3.83 (3H, s), 6.21 (1H, s), 6.79 to 7.56 (19H, m)

Example 74

Methyl 2-[bis(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) bis(3-fluorophenyl)methanol

[0235] To a solution (10 mL) of 3,3'-difluorobenzophenol (1.00 g, 4.58 mmol) in ethanol was added sodium borohydride (866 mg, 2.29 mmol), the mixture was stirred at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil.

982 mg (97.2%)

^{1}H-NMR ($CDCl_3$) δ; 2.31 (1H, d, J = 3.2 Hz), 5.81 (1H, d, J = 3.2 Hz), 6.92 to 7.37 (8H, m)

(2) Methyl 2-[bis(3-fluorophenyl)methoxy]-5-nitrobenzoate

[0236] A mixture of methyl 2-hydroxy-5-nitrobenzoate (413 mg, 2.09 mmol), bis(3-fluorophenyl)methanol (922 mg, 4.19 mmol), 40% solution of diethyl azodicarbonate in toluene (1.82 g, 4.19 mmol) and solution (5 mL) of triphenylphosphine (1.10 g, 4.19 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain the titled compound as a solid. 410 mg (49.2%)

^{1}H-NMR ($CDCl_3$) δ; 4.02 (3H, s), 6.38 (1H, s), 6.96 to 7.41 (9H, m), 8.22 (1 H, dd, J = 2.8, 9.2 Hz), 8.76 (1H, d, J = 2.8 Hz)

(3) Methyl 5-amino-2-[bis(3-fluorophenyl)methoxy]benzoate

[0237] Methyl 2-[bis(3-fluorophenyl)methoxy]-5-nitrobenzoate (400 mg, 1.00 mmol) and 5% iridium carbon (40 mg) were added thereto, and the mixture was stirred for 12 hours under hydrogen atmosphere at room temperature. The insolubles were filtered off, and the filtrate was concentrated. To the residue was added hexane, to obtain the titled compound as a solid. 188 mg (50.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.87 (3H, s), 6.09 (1H, s), 6.64 (2 H, d, J = 1.6 Hz), 6.90 to 7.35 (9H, m)

(4) Methyl 2-[bis(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0238] To a solution of methyl 5-amino-2-[bis(3-fluorophenyl)methoxy]benzoate (184 mg, 0.498 mmol) in THF (3 mL) was added 3,4-dimethoxyphenyl isocyanate (0.0889 mL, 0.598 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 106 mg (38.8%)

^{1}H-NMR ($CDCl_3$) δ; 3.81 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 6.14 (1H, s), 6.66 to 7.60 (16H, m)

IR (KBr) cm^{-1}; 3326, 1726, 1651, 1611, 1593, 1557, 1514, 1497, 1451, 1414, 1221, 1165, 1136, 1082, 1028, 772, 754, 733

Example 75

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-fluorophenyl)(phenyl)methoxy]benzoate

(1) (4-fluorophenyl)(phenyl)methanol

[0239] To a solution (100 mL) of p-fluorobenzophenol (10.0 g, 49.9 mmol) in ethanol was added sodium borohydride (945 mg, 25.0 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil.

9.63 g (96.3%)

^{1}H-NMR ($CDCl_3$) δ; 2.23 (1H, d, J = 3.8 Hz), 5.83 (1H, d, J = 3.8 Hz), 6.97 to 7.38 (9H, m)

(2) Methyl 2-[(4-fluorophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0240] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.62 g, 8.24 mmol), (4-fluorophenyl)(phenyl)methanol (2.00 g, 9.89 mmol), 40% solution of diethyl azodicarbonate in toluene (5.38 g, 12.4 mmol) and a solution (5 mL) of triphenylphosphine (2.59 g, 9.89 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain the titled compound as oil. 2.14 g (68.2%)

^{1}H-NMR ($CDCl_3$) δ; 3.98 (3H, s), 6.39 (1H, s), 6.98 to 7.52 (10H, m), 8.18 (1 H, dd, J = 3.0, 9.6 Hz), 8.72 (1H; d, J = 3.0 Hz)

IR (KBr) cm^{-1}; 1734, 1613, 1588, 1510, 1487, 1439, 1346, 1277, 1254, 1227, 1130, 1003, 824, 748, 698

(3) Methyl 5-amino-2-[(4-fluorophenyl)(phenyl)methoxy]benzoate

[0241] Methyl 2-[(4-fluorophenyl)(phenyl)methoxy]-5-nitrobenzoate (2.10 g, 5.50 mmol) and 5% iridium carbon (210 mg) were added thereto, and the mixture was stirred under hydrogen atmosphere at room temperature for 2 days. The insolubles were filtered off, and the filtrate was concentrated. To the residue was added hexane, to obtain the titled compound as oil. 1.87 g (96.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.49 (2H, bs), 3.83 (3H, s), 6.11 (1H, s), 6.58 to 7.48 (12H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-fluorophenyl)(phenyl)methoxy]benzoate

[0242] To a solution (10 mL) of methyl 5-amino-2-[(4-fluorophenyl)(phenyl)methoxy]benzoate (1.00 g, 2.85 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.509 mL, 3.42 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as a solid. 995 mg (65.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.20 (1H, s), 6.51 (1H, s), 6.61 (1H, s), 6.68 to 7.61 (15H, m)

Example 76

Methyl 2-[bis(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Bis(2-fluorophenyl)methanol

[0243] To a solution (200 mL) of 2-bromofluorobenzene (10.0 g, 57.1 mmol) in THF was added dropwise 1.6N solution of butyllithium in hexane (42.9 mL, 68.3 mmol) at -78°C, and the mixture was stirred at -78°C for 10 minutes. A solution (20 mL) of 2-fluorobenzaldehyde (7.09 g, 57.1 mmol) in THF was added dropwise to the mixture, and the mixture was stirred for 1 hour at -78 to -65°C. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as a solid. 4.14 g (32.9%)

^{1}H-NMR ($CDCl_3$) δ; 2.41 (1H, d, J = 4.6 Hz), 6.42 (1H, d, J = 4.6 Hz), 6.98 to 7.49 (8H, m)

(2) Methyl 2-[bis(2-fluorophenyl)methoxy]-5-nitrobenzoate

[0244] A solution (5 mL) of methyl 2-hydroxy-5-nitrobenzoate (1.49 g, 7.57 mmol), bis(2-fluorophenyl)methanol (2.00 g, 9.08 mmol), 40% solution of diethyl azodicarbonate in toluene (5.60 g, 12.9 mmol) and triphenylphosphine (2.38 g, 9.08 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 9:1), to obtain the titled compound as oil. 1.61 g (53.3%)

^{1}H-NMR ($CDCl_3$) δ; 3.98 (3H, s), 6.99 to 7.75 (10H, m), 8.26 (1 H, dd, J = 2.6, 9.4 Hz), 8.73 (1H, d, J = 2.6 Hz)

(3) Methyl 5-amino-2-[bis(2-fluorophenyl)methoxy]benzoate

[0245] Methyl 2-[bis(2-fluorophenyl)methoxy]-5-nitrobenzoate (1.55 g, 3.88 mmol) and 5% iridium carbon (200 mg) were added thereto, and the mixture was stirred under hydrogen atmosphere at room temperature for 2 days. The

insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as oil. 800 mg (55.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.48 (2H, bs), 3.83 (3H, s), 6.66 to 7.76 (12H, m)

(4) Methyl 2-[bis(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0246] To a solution (8 mL) of methyl 5-amino-2-[bis(2-fluorophenyl)methoxy]benzoate (780 mg, 2.11 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.377 mL, 2.53 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate, to obtain the titled compound as a solid. 1.08 g (93.1%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.48 to 7.75 (17H, m)

Example 77

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-fluorophenyl)(4-fluorophenyl)methoxy]benzoate

(1) (2-Fluorophenyl)(4-fluorophenyl)methanol

[0247] To a solution (100 mL) of 2,4'-difluorobenzophenol (10.0 g, 45.8 mmol) in ethanol was added sodium borohydride (867 mg, 22.9 mmol), the mixture was stirred at room temperature for 2 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.88 g (97.8%)

^{1}H-NMR ($CDCl_3$) δ; 2.32 (1H, d, J = 4.0 Hz), 5.83 (1H, d, J = 4.0 Hz), 6.95 to 7.53 (8H, m)

(2) Methyl 2-[(2-fluorophenyl)(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0248] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.23 g, 11.3 mmol), (2-fluorophenyl)(4-fluorophenyl)methanol (3.00 g, 13.6 mmol), 40% solution of diethyl azodicarbonate in toluene (7.87 g, 18.1 mmol) and a solution (5 mL) of triphenylphosphine (3.56 g, 13.6 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 9:1), to obtain the titled compound as a solid. 2.00 g (48.0%)

^{1}H-NMR ($CDCl_3$) δ; 3.99 (3H, s), 6.78 (1H, s), 7.01 to 7.70 (9H, m), 8.23 (1 H, dd, J = 2.6, 9.2 Hz), 8.74 (1H, d, J = 2.6 Hz)

(3) Methyl 5-amino-2-[(2-fluorophenyl)(4-fluorophenyl)methoxy]benzoate

[0249] To a solution (100 mL) of methyl 2-[(2-fluorophenyl)(4-fluorophenyl)methoxy]-5-nitrobenzoate (2.00 g, 5.01 mmol) in ethyl acetate was added 5% iridium carbon (200 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 2 days. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as oil. 1.79 g (96.8%)

^{1}H-NMR ($CDCl_3$) δ; 3.85 (3H, s), 6.49 (1H, s), 6.62 to 7.75 (11H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-fluorophenyl)(4-fluorophenyl)methoxy]benzoate

[0250] To a solution (60 mL) of methyl 5-amino-2-[(2-fluorophenyl)(4-fluorophenyl)methoxy]benzoate (1.74 g, 4.71 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.841 mL, 5.65 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. This was recrystallized from hexane and ethyl acetate. 743 mg (28.8%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 6.55 to 7.66 (17H, m)

Example 78

Methyl 2-[(2,6-difluorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) (2,6-Difluorophenyl)(phenyl)methanol

[0251] To a solution (100 mL) of 2,6-difluorobenzophenol (10.0 g, 45.8 mmol) in ethanol was added sodium borohydride (867 mg, 22.9 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.80 g (97.0%)

^{1}H-NMR ($CDCl_3$) δ; 2.75 - 2.82 (1H, m), 6.24 (1H, d, J = 8.8 Hz), 6.84 to 7.42 (8H, m)

(2) Methyl 2-[(2, 6-difluorophenyl)(phenyl)methoxy]-5-nitrobenzoate (16d)

[0252] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.23 g, 11.3 mmol), (2, 6-difluorophenyl)(phenyl)methanol (3.00 g, 13.6 mmol), 40% solution of diethyl azodicarbonate in toluene (7.87 g, 18.1 mmol) and a solution (5 mL) of triphenylphosphine (3.56 g, 13.6 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as a solid. 410 mg (9.10%)

^{1}H-NMR ($CDCl_3$) δ; 3.99 (3H, s), 6.86 to 7.63 (10H, m), 8.24 (1 H, dd, J = 3.0, 9.2 Hz), 8.72 (1H, d, J = 3.0 Hz)

(3) Methyl 5-amino-2-[(2, 6-difluorophenyl)(phenyl)methoxy]benzoate (17d)

[0253] To a solution (20 mL) of methyl 2-[(2, 6-difluorophenyl)(phenyl)methoxy]-5-nitrobenzoate (400 mg, 1.00 mmol) in ethyl acetate was added 5% iridium carbon (50 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 2 days. The insolubles were filtered off, and the filtrate was concentrated. To the residue was added hexane, to obtain the titled compound as oil. 360 mg (97.3%)

H-NMR ($CDCl_3$) δ; 3.52 (2H, bs), 3.82 (3H, s), 6.11 (1H, s), 6.598 to 7.61 (12H, m)

(4) Methyl 2-[(2, 6-difluorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0254] To a solution (4 mL) of methyl 5-amino-2-[(2, 6-difluorophenyl)(phenyl)methoxy]benzoate (350 mg, 0.948 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.169 mL, 1.14 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 467 mg (87.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.50 to 7.59 (17H, m)

Example 79

Methyl 2-[(4-chlorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) (4-Chlorophenyl)(phenyl)methanol

[0255] To a solution (100 mL) of 4-chlorobenzophenol (10.0 g, 46.2 mmol) in ethanol and THF (10 mL) was added sodium borohydride (876 mg, 23.1 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 8.90 g (88.8%)

^{1}H-NMR ($CDCl_3$) δ; 2.20 (1H, d, J = 3.2 Hz), 5.82 (1H, d, J = 3.2 Hz), 7.26 to 7.36 (9H, m)

(2) Methyl 2-[(4-chlorophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0256] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.25 g, 11.4 mmol), (4-chlorophenyl)(phenyl)methanol (3.00 g, 13.7 mmol), 40% solution of diethyl azodicarbonate in toluene (7.95 g, 18.3 mmol) and a solution (8 mL) of triphenylphosphine (3.59 g, 13.7 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was

poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 4.43 g (97.6%)

^{1}H-NMR ($CDCl_3$) δ; 3.98 (3H, s), 6.38 (1H, s), 6.99 (1H, d, J = 9.4 Hz), 7.26 to 7.50 (9H, m), 8.19 (1 H, dd, J = 2.6, 9.4 Hz), 8.73 (1H, d, J = 2.6 Hz)

(3) Methyl 5-amino-2-[(4-chlorophenyl)(phenyl)methoxy]benzoate

[0257] A mixture of methyl 2-[(4-chlorophenyl)(phenyl)methoxy]-5-nitrobenzoate (2.00 g, 5.03 mmol), iron (1.40 g, 25.1 mmol) and calcium chloride (279 mg, 2.52 mmol) in ethanol (32 mL) and water (8 mL) was heated to reflux for 2 hours, the insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1 :1), to obtain the titled compound as oil. 900 mg (48.6%)

^{1}H-NMR ($CDCl_3$) δ; 3.48 (2H, bs), 3.83 (3H, s), 6.09 (1H, s), 6.62 to 6.63 (2H, m), 7.12 to 7.46 (10H, m)

(4) Methyl 2-[(4-chlorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0258] To a solution (20 mL) of methyl 5-amino-2-[(4-chlorophenyl)(phenyl)methoxy]benzoate (900 mg, 2.45 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.437 mL, 2.94 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as a solid. 662 mg (49.4%)

^{1}H-NMR ($CDCl_3$) δ; 3.72 (3H, s), 3.74 (3H, s), 3.80 (3H, s), 6.09 (1H, s), 6.60 to 7.61 (17H, m)

Example 80

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-fluorophenyl)(phenyl)methoxy]benzoate

(1) (2-Fluorophenyl)(phenyl)methanol

[0259] To a solution (100 mL) of p-fluorobenzophenol (10.0 g, 49.9 mmol) in ethanol was added sodium borohydride (945 mg, 25.0 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.80 g (97.0%)

^{1}H-NMR ($CDCl_3$) δ; 2.31 (1H, d, J = 4.8 Hz), 6.14 (1H, d, J = 4.8 Hz), 6.96 to 7.55 (9H, m)

(2) Methyl 2-[(2-fluorophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0260] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.42 g, 12.3 mmol), (2-fluorophenyl)(phenyl)methanol (3.00 g, 14.8 mmol), 40% solution of diethyl azodicarbonate (8.31 g, 19.7 mmol) and a solution (8 mL) of triphenylphosphine (3.88 g, 14.8 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as a solid. 2.88 g (61.4%)

^{1}H-NMR ($CDCl_3$) δ; 4.00 (3H, s), 6.79 (1H, s), 6.96 to 7.73 (10H, m), 8.21 (1 H, dd, J = 2.8, 9.2 Hz), 8.73 (1H, d, J = 2.8 Hz)

(3) Methyl 5-amino-2-[(2-fluorophenyl)(phenyl)methoxy]benzoate

[0261] A mixture of methyl 2-[(2-fluorophenyl)(phenyl)methoxy]-5-nitrobenzoate (2.87 g, 7.53 mmol), iron (2.10 g, 37.7 mmol) and calcium chloride (418 mg, 3.77 mmol) in ethanol (54 mL) and water (13 mL) was stirred at 100°C for 5 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as oil. 1.89 g (71.3%)

^{1}H-NMR ($CDCl_3$) δ; 3.46 (2H, bs), 3.85 (3H, s), 6.52 (1H, s), 6.61 to 7.77 (12H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-fluorophenyl)(phenyl)methoxy]benzoate

[0262] To a solution (10 mL) of methyl 5-amino-2-[(2-fluorophenyl)(phenyl)methoxy]benzoate (1.87 g, 5.33 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.951 mL, 6.39 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 1.77 g (62.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.89 (3H, s), 6.55 to 7.70 (18H, m)

Example 81

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate

(1) (4-Trifluoromethylphenyl)(phenyl)methanol

[0263] To a solution (50 mL) of 4-trifluoromethylbenzophenol (5.00 g, 20.0 mmol) in ethanol was added sodium borohydride (378 mg, 10.0 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 4.85 g (96.2%)

^{1}H-NMR ($CDCl_3$) δ; 2.36 (1H, d, J = 3.2 Hz), 5.87 (1H, d, J = 3.2 Hz), 7.25 to 7.34 (5H, m), 7.50 (2H, d, J = 8.4 Hz), 7.58 (2H, d, J = 8.4 Hz)

(2) Methyl 2-[(4-trifluoromethylphenyl)(phenyl)methoxy]-5-nitrobenzoate

[0264] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.93 g, 9.81 mmol), (4-trifluoromethylphenyl)(phenyl)methanol (3.00 g, 11.8 mmol), 40% solution of diethyl azodicarbonate in toluene (6.83 g, 15.7 mmol) and a solution (8 mL) of triphenylphosphine (3.09 g, 11.8 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 3.37 g (79.7%)

^{1}H-NMR ($CDCl_3$) δ; 4.00 (3H, s), 6.46 (1H, s), 7.00 (1H, d, J = 9.2 Hz), 7.26 to 7.72 (9H, m), 8.20 (1 H, dd, J = 3.0, 9.2 Hz), 8.74 (1H, d, J = 3.0 Hz)

(3) Methyl 5-amino-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate

[0265] A mixture of methyl 2-[(4-trifluoromethylphenyl)(phenyl)methoxy]-5-nitrobenzoate (3.30 g, 7.65 mmol), iron (2.14 g, 38.3 mmol) and calcium chloride (425 mg, 3.83 mmol) in ethanol (50 mL) and water (12 mL) was stirred at 100°C for 3 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as oil. 2.06 g (67.1%)

^{1}H-NMR ($CDCl_3$) δ; 3.46 (2H, bs), 3.84 (3H, s), 6.16 (1H, s), 6.62 to 6.64 (2H, m), 7.13 to 7.67 (10H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate

[0266] To a solution (50 mL) of methyl 5-amino-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate (2.00 g, 4.98 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.890 mL, 5.98 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as a solid. 1.87 g (64.7%)

^{1}H-NMR ($CDCl_3$) δ; 3.81 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 6.23 (1H, s), 6.66 to 7.66 (17H, m)

Example 82

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(phenyl)methoxy]benzoate

(1) (2-Chlorophenyl)(phenyl)methanol

[0267] To a solution (100 mL) of 2-chlorobenzophenol (10.0 g, 46.2 mmol) in ethanol was added sodium borohydride (876 mg, 23.1 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under

reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.50 g (94.1%)

^{1}H-NMR ($CDCl_3$) δ; 2.35 (1H, d, J = 4.0 Hz), 6.22 (1H, d, J = 4.0 Hz), 7.18 to 7.63 (9H, m)

(2) Methyl 2-[(2-chlorophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0268] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.25 g, 11.4 mmol), (2-chlorophenyl)(phenyl)methanol (3.00 g, 13.7 mmol), 40% solution of diethyl azodicarbonate in toluene (7.95 g, 18.3 mmol) and a solution (8 mL) of triphenylphosphine (3.59 g, 13.7 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as a solid. 2.84 g (62.6%)

^{1}H-NMR ($CDCl_3$) δ; 3.98 (3H, s), 6.90 (1H, s), 7.02 (1H, d, J = 9.0 Hz), 7.25 to 7.76 (9H, m), 8.23 (1 H, dd, J = 2.8, 9.0 Hz), 8.72 (1H, d, J = 2.8 Hz)

(3) Methyl 5-amino-2-[(2-chlorophenyl)(phenyl)methoxy]benzoate

[0269] A mixture of methyl 2-[(2-chlorophenyl)(phenyl)methoxy]-5-nitrobenzoate (2.80 g, 7.04 mmol), iron (1.97 g, 35.2 mmol) and calcium chloride (391 mg, 3.52 mmol) in ethanol (50 mL) and water (13 mL) was stirred at 100°C for 4 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as a solid. 1.23 g (47.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.45 (2H, bs), 3.85 (3H, s), 6.63 to 6.73 (3H, m), 7.12 to 7.83 (10H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(phenyl)methoxy]benzoate

[0270] To a solution (50 mL) of methyl 5-amino-2-[(2-chlorophenyl)(phenyl)methoxy]benzoate (1.20 g, 3.26 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.582 mL, 3.91 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 1.70 g (95.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.85 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 6.42 (1H, s), 6.52 (1H, s), 6.73 to 7.78 (16H, m)

Example 83

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2,4-dichlorophenyl)(phenyl)methoxy]benzoate

(1) (2,4-Dichlorophenyl)(phenyl)methanol

[0271] To a solution of 2,4-dichlorobenzophenol (10.0 g, 39.8 mmol) in ethanol (100 mL) and THF (100 mL) was added sodium borohydride (753 mg, 19.9 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.40 g (93.0%)

^{1}H-NMR ($CDCl_3$) δ; 2.34 (1H, d, J = 3.6 Hz), 6.15 (1H, d, J = 3.6 Hz), 7.25 to 7.37 (7H, m), 7.57 (1H, d, J = 8.4 Hz)

(2) Methyl 2-[(2,4-dichlorophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0272] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.96 g, 9.92 mmol), (2,4-dichlorophenyl)(phenyl)methanol (3.00 g, 11.9 mmol), 40% solution of diethyl azodicarbonate in toluene (5.17 g, 11.9 mmol) and a solution (8 mL) triphenylphosphine (3.12 g, 11.9 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 4.00 g (93.2%)

^{1}H-NMR ($CDCl_3$) δ; 3.97 (3H, s), 6.83 (1H, s), 7.00 (1H, d, J = 9.2 Hz), 7.24 to 7.74 (8H, m), 8.24 (1 H, dd, J = 2.8, 9.2 Hz), 8.72 (1H, d, J = 2.8 Hz)

(3) Methyl 5-amino-2-[(2,4-dichlorophenyl)(phenyl)methoxy]benzoate

[0273] A mixture of methyl 2-[(2,4-dichlorophenyl)(phenyl)methoxy]-5-nitrobenzoate (4.00 g, 9.25 mmol), iron (2.58 g, 46.3 mmol) and calcium chloride (513 mg, 4.63 mmol) in ethanol (64 mL) and water (16 mL) was stirred at 100°C for 5 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 5:1), to obtain the titled compound as a solid. 860 mg (24.1%)

^{1}H-NMR ($CDCl_3$) δ; 3.47 (2H, bs), 3.84 (3H, s), 6.56 (1H, s), 6.67 to 7.80 (11H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2,4-dichlorophenyl)(phenyl)methoxy]benzoate

[0274] To a solution (10 mL) of methyl 5-amino-2-[(2,4-dichlorophenyl)(phenyl)methoxy]benzoate (840 mg, 2.17 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.388 mL, 2.61 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 970 mg (77.0%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 6.64 to 7.74 (17H, m)

Example 84

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4'-chlorophenyl)methoxy]benzoate

(1) (2-Chlorophenyl)(4'-chlorophenyl)methanol

[0275] To a solution of 2,4'-dichlorobenzophenone (10.0 g, 39.8 mmol) in ethanol (100 mL) and THF (100 mL) was added sodium borohydride (753 mg, 19.9 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.43 g (93.4%)

^{1}H-NMR ($CDCl_3$) δ; 2.39 (1H, d, J = 3.8 Hz), 6.20 (1H, d, J = 3.8 Hz), 7.18 to 7.58 (8H, m)

(2) Methyl 2-[(2 -chlorophenyl)(4'-chlorophenyl)methoxy]-5-nitrobenzoate

[0276] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.96 g, 9.92 mmol), (2 -chlorophenyl)(4'-chlorophenyl)methanol (3.00 g, 11.9 mmol), 40% solution of diethyl azodicarbonate in toluene (5.17 g, 11.9 mmol) and a solution (8 mL) of triphenylphosphine (3.12 g, 11.9 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 2.83 g (65.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.99 (3H, s), 6.87 (1H, s), 6.98 (1H, d, J = 9.0 Hz), 7.05 to 7.71 (8H, m), 8.23 (1 H, dd, J = 2.4, 9.0 Hz), 8.73 (1H, d, J = 2.4 Hz)

(3) Methyl 5-amino-2-[(2-chlorophenyl)(4'-chlorophenyl)methoxy]benzoate

[0277] A mixture of methyl 2-[(2-dichlorophenyl)(4'-chlorophenyl)methoxy]-5-nitrobenzoate (2.80 g, 6.47 mmol), iron (2.02 g, 36.3 mmol) and calcium chloride (402 mg, 3.63 mmol) in ethanol (50 mL) and water (13 mL) was stirred at 100°C for 5 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 5:1), to obtain the titled compound as oil. 1.88 g (75.2%)

^{1}H-NMR ($CDCl_3$) δ; 3.47 (2H, bs), 3.84 (3H, s), 6.59 (1H, s), 6.66 to 6.67 (2H, m), 7.13 to 7.79 (9H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4'-chlorophenyl)methoxy]benzoate

[0278] To a solution (20 mL) of methyl 5-amino-2-[(2-dichlorophenyl)(4'-chlorophenyl)methoxy]benzoate (1.83 g, 4.74 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.846 mL, 5.69 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, was poured into water, and was extracted with ethyl acetate. The solvent was distilled off under reduced pressure, the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 1.58 g (57.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.48 (1H, s), 6.59 (1H, s), 6.68 to 7.74 (15H, m)

Example 85

Methyl 5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(3-chlorophenyl)(phenyl)methoxy]benzoate

(1) (3-Chlorophenyl)(phenyl)methanol

[0279] To a solution of 3-chlorobenzophenone (10.0 g, 46.2 mmol) in ethanol (100 mL) and THF (100 mL) was added sodium borohydride (876 mg, 23.1 mmol), the mixture was stirred at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as oil. 9.53 g (94.4%)

^{1}H-NMR ($CDCl_3$) δ; 2.55 (1H, d, J = 3.6 Hz), 5.80 (1H, d, J = 3.6 Hz), 7.25 to 7.40 (9H, m)

(2) Methyl 2-[(3-chlorophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0280] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.25 g, 11.4 mmol), (3-chlorophenyl)(phenyl)methanol (3.00 g, 13.7 mmol), 40% solution of diethyl azodicarbonate in toluene (7.95 g, 18.3 mmol) and a solution (8 mL) of triphenylphosphine (3.59 g, 13.7 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as a solid. 3.06 g (67.4%)

^{1}H-NMR ($CDCl_3$) δ; 4.01 (3H, s), 6.37 (1H, s), 6.99 (1H, d, J = 9.4 Hz), 7.23 to 7.57 (9H, m), 8.20 (1 H, dd, J = 3.0, 9.4 Hz), 8.74 (1H, d, J = 3.0 Hz)

(3) Methyl 5-amino-2-[(3-chlorophenyl)(phenyl)methoxy]benzoate

[0281] A mixture of methyl 2-[(3-chlorophenyl)(phenyl)methoxy]-5-nitrobenzoate (2.90 g, 7.29 mmol), iron (2.04 g, 36.4 mmol) and calcium chloride (405 mg, 3.65 mmol) in ethanol (50 mL) and water (13 mL) was stirred at 100°C for 5 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as oil. 2.36 g (88.1%)

^{1}H-NMR ($CDCl_3$) δ; 3.48 (2H, bs), 3.86 (3H, s), 6.08 (1H, s), 6.62 to 7.55 (12H, m)

(4) Methyl 5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(3-chlorophenyl)(phenyl)methoxy]benzoate

[0282] To a solution (50 mL) of methyl 5-amino-2-[(3-chlorophenyl)(phenyl)methoxy]benzoate (2.30 g, 6.25 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (1.12 mL, 7.50 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ethyl acetate. 2.63 g (77.1%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.90 (3H, s), 6.16 (1H, s), 6.57 to 7.61 (17H, m)

Example 86

N-(tert-Butyl)-5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzamide

[0283] A mixture of 5-({[[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzoic acid (500 mg, 0.883 mmol), 1-hydroxy-1H-benzotriazole (203 mg, 1.33 mmol), tert-butyl amine (0.186 mL, 1.77 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (212 mg, 1.10 mmol), and a solution (5 mL) in DMF was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 472 mg (86.0%)

^{1}H-NMR ($CDCl_3$) δ; 1.17 (9H, s), 3.81 (3H, s), 3.83 (3H, s), 6.29 (1H, s), 6.71 to 7.73 (18H, m)

Example 87

Methyl 5-({[(4-hydroxy-3-methoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzoate

(1) 4-Amino-2-methoxyphenol

[0284] A mixture of 2-methoxy-4-nitrophenol (3.00 g, 17.7 mmol), 10% palladium carbon (300 mg), THF (100 mL) and methanol (100 mL) was stirred under hydrogen atmosphere at room temperature for 4 hours.

[0285] The insolubles were filtered off, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 2.32 g (94.3%)

^{1}H-NMR ($CDCl_3$) δ; 3.40 (2H, bs), 5.50 (1H, bs), 6.21 (1H, dd, J = 8.2, 2.6Hz), 6.30 (1H, d, J = 2.6 Hz), 8.72 (1H, d, J = 8.2 Hz)

(2) Methyl 5-({[(4-hydroxy-3-methoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzoate

[0286] A solution (9 mL) of methyl 5-amino-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate (300 mg, 0.748 mmol), diisopropylethyl amine (0.149 mL, 0.898 mmol) and di(N-succinimidyl) carbonate (230 mg, 0.898 mmol) in acetonitrile was stirred for 1 hour under ice-cooling, diisopropylethyl amine (0.149 mL, 0.898 mmol) and 4-amino-2-methoxyphenol (125 mg, 0.898 mmol) were added to the solution under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours.

[0287] The reaction mixture was poured into water, was extracted with ethyl acetate, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1: 1), to obtain the titled compound as a solid. 67.2 mg (15.8%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.88 (3H, s), 5.56 (1H, s), 6.25 (1H, s), 6.50 to 7.67 (17H, m)

Example 88

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(3-trifluoromethylphenyl)(phenyl)methoxy]benzoate

(1) Methyl 2-[(3-trifluoromethylphenyl)(phenyl)methoxy]-5-nitrobenzoate

[0288] A mixture of methyl 2-hydroxy-5-nitrobenzoate (651 mg, 3.30 mmol), (3-trifluoromethylphenyl)(phenyl)methanol (1.00 g, 3.96 mmol), 40% solution of diethyl azodicarbonate in toluene (2.30 g, 5.29 mmol) and a solution (1 mL) of triphenylphosphine (1.04 g, 3.96 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 1.39 g (97.9%)

^{1}H-NMR ($CDCl_3$) δ; 4.01 (3H, s), 6.46 (1H, s), 7.02 (1H, d, J = 9.2 Hz), 7.26 to 7.88 (9H, m), 8.20 (1 H, dd, J = 3.0, 9.2 Hz), 8.75 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-[(3-trifluoromethylphenyl)(phenyl)methoxy]benzoate

[0289] A mixture of methyl 2-[(3-trifluoromethylphenyl)(phenyl)methoxy]-5-nitrobenzoate (1.36 g, 3.16 mmol), iron (882 mg, 15.8 mmol) and calcium chloride (175 mg, 1.58 mmol) in ethanol (20 mL) and water (5 mL) was stirred at 100°C for 4 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as oil. 880 mg (69.3%)

^{1}H-NMR ($CDCl_3$) δ; 3.49 (2H, bs), 3.85 (3H, s), 6.17 (1H, s), 6.62 to 6.64 (2H, m), 7.14 to 7.84 (10H, m)

(3) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(3-trifluoromethylphenyl)(phenyl)methoxy]benzoate

[0290] To a solution (10 mL) of methyl 5-amino-2-[(3-trifluoromethylphenyl)(phenyl)methoxy]benzoate (860 mg, 2.14 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.383 mL, 2.57 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 12:1), to obtain the titled compound as a solid. 815 mg (65.7%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 6.25 (1H, s), 6.59 (1H, s), 6.70 to 7.68 (15H, m), 7.87

(1H, s)

Example 89

Methyl 2-{bis[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Bis[4-(trifluoromethyl)phenyl]methanol

[0291] To a solution (200 mL) of 2-bromo-4-trifluoromethylbenzene (10.0 g, 44.4 mmol) in THF was added dropwise 1.6N solution of butyllithium in hexane (33.2 mL, 53.1 mmol) at -78°C, and the mixture was stirred at -78°C for 10 minutes. A solution (20 mL) of 4-trifluoromethyl benzaldehyde (9.24 g, 53.1 mmol) in THF was added dropwise to the mixture, and the mixture was stirred at -78 to -65°C for 1 hour. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as oil. 8.50 g (59.9%)

^{1}H-NMR ($CDCl_3$) δ; 2.51 (1H, d, J = 3.0 Hz), 5.94 (1H, d, J = 3.0 Hz), 7.49 (4H, d, J = 8.1 Hz), 7.60 (4H, d, J = 8.1 Hz)

(2) Methyl 2-{bis[4-(trifluoromethyl)phenyl)methoxy}-5-nitrobenzoate

[0292] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.54 g, 7.82 mmol), bis[4-(trifluoromethyl)phenyl]methanol (3.00 g, 9.38 mmol), 40% solution of diethyl azodicarbonate in toluene (5.45 g, 12.5 mmol) and a solution (5 mL) of triphenylphosphine (2.46 g, 9.38 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 2.23 g (63.5%)

^{1}H-NMR ($CDCl_3$) δ; 4.01 (3H, s), 6.52 (1H, s), 6.97 (1H, d, J = 9.2 Hz), 7.59 to 7.72 (8H, m), 8.43 (1 H, dd, J = 3.0, 9.2 Hz), 8.77 (1H, d, J = 3.0 Hz)

(3) Methyl 5-amino-2-{bis[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0293] A mixture of methyl 2-{bis[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate (2.22 g, 4.94 mmol), iron (1.38 g, 24.7 mmol) and calcium chloride (274 mg, 2.47 mmol) in ethanol (30 mL) and water (7.5 mL) was stirred at 100°C for 4 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 3:1), to obtain the titled compound as oil. 1.23 g (53.0%)

^{1}H-NMR ($CDCl_3$) δ; 3.52 (2H, bs), 3.84 (3H, s), 6.23 (1H, s), 6.62 to 6.63 (2H, m), 7.16 to 7.17 (1H, m), 7.56 to 7.61 (8H, m)

(4) Methyl 2-{bis[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0294] To a solution (20 mL) of methyl 5-amino-2-{bis[4-(trifluoromethyl)phenyl]methoxy}benzoate (1.22 g, 2.60 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.464 mL, 3.12 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 1.09 g (64.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 6.29 (1H, s), 6.59 to 7.64 (16H, m)

Example 90

Methyl 2-{(4-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

(1) (4-Chlorophenyl)[4-(trifluoromethyl)phenyl]methanol

[0295] To a solution (200 mL) of 4-bromochlorobenzene (10.0 g, 52.2 mmol) in THF was added dropwise 1.6N solution of butyllithium in hexane (39.2 mL, 62.6 mmol) at -78°C, and the mixture was stirred at -78°C for 10 minutes. A solution (30 mL) of 4-trifluoromethyl benzaldehyde (10.9 g, 62.6 mmol) in THF was added dropwise to the mixture, and the mixture was stirred at -78 to -65°C for 1 hour. The reaction solution was poured into an aqueous solution of saturated

ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 7: 1), to obtain the titled compound as oil. 6.70 g (44.7%)

^{1}H-NMR ($CDCl_3$) δ; 2.29 (1H, d, J = 3.0 Hz), 5.87 (1H, d, J = 3.0 Hz), 7.26 to 7.36 (4H, m), 7.48 (2H, d, J = 7.8 Hz), 7.60 (2H, d, J = 7.8 Hz)

(2) Methyl 2-{(4-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0296] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.72 g, 8.75 mmol), (4-chlorophenyl)[4-(trifluoromethyl)phenyl]methanol (3.00 g, 10.5 mmol), 40% solution of diethyl azodicarbonate in toluene (6.09 g, 14.0 mmol) and a solution (5 mL) of triphenylphosphine (2.75 g, 10.5 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 2.58 g (63.2%)

^{1}H-NMR ($CDCl_3$) δ; 4.00 (3H, s), 6.45 (1H, s), 6.97 (1H, d, J = 9.2 Hz), 7.26 to 7.70 (8H, m), 8.22 (1 H, dd, J = 3.0, 9.2 Hz), 8.76 (1H, d, J = 3.0 Hz)

(3) Methyl 5-amino-2-{(4-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0297] A mixture of methyl 2-{(4-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate (2.50 g, 5.37 mmol), iron (1.50 g, 26.9 mmol) and calcium chloride (296 mg, 2.68 mmol) in ethanol (34 mL) and water (9 mL) was stirred at 100°C for 4 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1: 1), to obtain the titled compound as oil. 850 mg (36.3%)

^{1}H-NMR ($CDCl_3$) δ; 3.52 (2H, bs), 3.84 (3H, s), 6.14 (1H, s), 6.61 to 6.63 (2H, m), 7.14 to 7.16 (1H, m), 7.29 (2H, d, J = 8.8 Hz), 7.40 (2H, d, J = 8.8 Hz), 7.60 (4H, s)

(4) Methyl 2-{(4-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0298] To a solution (10 mL) of methyl 5-amino-2-{(4-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate (830 mg, 1.90 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.340 mL, 2.29 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 810 mg (69.2%)

^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.23 (1H, s), 6.52 (1H, s), 6.64 (1H, s), 6.69 to 7.64 (14H, m)

Example 91

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy} benzoate

(1) (4-Fluorophenyl)[4-(trifluoromethyl)phenyl]methanol

[0299] To a solution (200 mL) of 4-bromofluorobenzene(10.0 g, 57.1 mmol) in THF was added dropwise 1.6N solution of butyllithium in hexane (42.8 mL, 68.5 mmol) at -78°C, and the mixture was stirred at -78°C for 10 minutes. A solution (30 mL) of 4-trifluoromethyl benzaldehyde (11.9 g, 68.5 mmol) in THF was added dropwise to the mixture, and the mixture was stirred at -78 to -65°C for 1 hour. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 10:1), to obtain the titled compound as oil. 7.00 g (45.5%)

^{1}H-NMR ($CDCl_3$) δ; 2.37 (1H, d, J = 3.2 Hz), 5.87 (1H, d, J = 3.2 Hz), 6.99 to 7.08 (2H, m), 7.26 to 7.35 (2H, m), 7.48 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz)

(2) Methyl 2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0300] A mixture of methyl 2-hydroxy-5-nitrobenzoate (1.82 g, 9.25 mmol), (4-fluorophenyl)[4-(trifluoromethyl)phenyl]

methanol (3.00 g, 11.1 mmol), 40% solution of diethyl azodicarbonate in toluene (6.44 g, 14.8 mmol) and a solution (5 mL) of triphenylphosphine (2.91 g, 11.1 mmol) in DMF was stirred at room temperature for 12 hours, and the reaction solution was poured into ice-water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 2.74 g (65.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.99 (3H, s), 6.46 (1H, s), 6.96 to 7.65 (9H, m), 8.22 (1 H, dd, J = 2.8, 9.2 Hz), 8.76 (1H, d, J = 2.8 Hz)

(3) Methyl 5-amino-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0301] A mixture of methyl 2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate (2.70 g, 6.00 mmol), iron (1.68 g, 30.0 mmol) and calcium chloride (333 mg, 3.00 mmol) in ethanol (40 mL) and water (10 mL) was stirred at 100°C for 4 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as oil. 1.66 g (65.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.49 (2H, bs), 3.84 (3H, s), 6.16 (1H, s), 6.62 to 7.60 (11H, m)

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy} benzoate

[0302] To a solution (10 mL) of methyl 5-amino-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate (1.63 g, 3.89 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.694 mL, 4.66 mmol) under ice-cooling, the mixture was stirred at 0°C for 2 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 1.41 g (60.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 6.23 (1H, s), 6.57 to 7.63 (16H, m)

Example 92

5-({[(3,4-Dimethoxyphenyl)amino]carbonyl}amino)-N-isopropyl-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzamide

[0303] A mixture of 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzoic acid (300 mg, 0.530 mmol), 1-hydroxy-1H-benzotriazole (122 mg, 0.798 mmol),isopropyl amine (0.0903 mL, 1.06 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (126 mg, 0.660 mmol) and DMF (3 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. This was recrystallized from hexane and ethyl acetate. 264 mg (82.0%)

^{1}H-NMR ($CDCl_3$) δ; 0.87 to 0.93 (6H, m), 3.85 (6H, s), 4.06 to 4.16 (1H, m), 6.33 (1H, s), 6.68 to 8.03 (18H, m)

Example 93

5-({[(3,4-Dimethoxyphenyl)amino]carbonyl}amino)-N-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-{phenyl [4-(trifluoromethyl)phenyl]methoxy}benzamide

[0304] A mixture of 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy} benzoic acid (300 mg, 0.530 mmol), 1-hydroxy-1H-benzotriazole (122 mg, 0.798 mmol), 2,2-dimethyltetrahydro-2H-pyran-4-yl amine (137 mg, 1.06 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (126 mg, 0.660 mmol) and DMF (3 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as a solid. This was recrystallized from hexane and ethyl acetate. 315 mg (87.7%)

^{1}H-NMR ($CDCl_3$) δ; 0.66 to 1.07 (8H, m), 1.27 to 1.86 (2H, m), 3.32 to 3.60 (2H, m), 3.84 (6H, s), 4.02 to 4.19 (1H, m), 6.32 (1H, s), 6.66 to 7.98 (18H, m)

Example 94

Methyl 5-({[(6-methoxypyridin-3-yl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0305] A solution of methyl 5-amino-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate (300 mg, 0.748 mmol), diisopropylethyl amine (0.149 mL, 0.898 mmol), di(N-succinimidyl) carbonate (230 mg, 0.898 mmol) and acetonitrile (9 mL) was stirred for 1 hour under ice-cooling, diisopropylethyl amine (0.149 mL, 0.898 mmol) and 5-amino-2-methoxypyridine (111 mg, 0.898 mmol) were added to the mixture under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours.

[0306] The reaction mixture was poured into water, was extracted with ethyl acetate, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as oil. 235 mg (56.9%)

^{1}H-NMR ($CDCl_3$) δ; 3.88 (6H, s), 6.26 (1H, s), 6.68 to 7.70 (16H, m), 7.98 (1H, d, J = 2.4 Hz)

Example 95

Methyl 5-[({[4-methoxy-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0307] A solution of methyl 5-amino-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate (300 mg, 0.748 mmol), diisopropylethyl amine (0.149 mL, 0.898 mmol), di(N-succinimidyl) carbonate (230 mg, 0.898 mmol) and acetonitrile (9 mL) was stirred for 1 hour under ice-cooling, diisopropylethyl amine (0.149 mL, 0.898 mmol) and 5-amino-2-methoxybenzotrifluoride (172 mg, 0.898 mmol) were added to the solution under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours. The reaction solution was poured into water, extracted with ethyl acetate, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 247 mg (53.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.82 (3H, s), 3.88 (3H, s), 6.24 (1H, s), 6.73 to 7.66 (17H, m)

Example 96

Methyl 5-({[(3-fluoro-4-methoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0308] A solution of methyl 5-amino-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate (300 mg, 0.748 mmol), diisopropylethyl amine (0.149 mL, 0.898 mmol), di(N-succinimidyl) carbonate (230 mg, 0.898 mmol) and acetonitrile (9 mL) was stirred for 1 hour under ice-cooling, diisopropylethyl amine (0.149 mL, 0.898 mmol) and 3-fluoro-4 aniline (127 mg, 0.898 mmol) were added to the solution under ice-cooling, and the mixture was stirred under ice-cooling for 1 hour and at room temperature for 12 hours. The reaction solution was poured into water, extracted with ethyl acetate, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as a solid. 287 mg (67.5%)

^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.88 (3H, s), 6.25 (1H, s), 6.63 to 7.67 (17H, m)

Synthetic method of amide derivatives by combinatorial synthesis

[0309] The compounds of Examples 97 to 143 were synthesized according to the followings.

[0310] To a mixed solution of 5-(anilinocarbonylamino)-2-benzhydryloxy benzoic acid (0.0684 mmol), 1-hydroxy-7-azabenzotriazole (0.0821 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.1026 mmol) in DMF (0.3 mL) and dichloromethane (0.7 mL) was added amine (0.0821 mmol), the mixture was stirred at room temperature for 2 hours, water and dichloromethane were added to the mixture, the layer of dichloromethane was separated by PTFE filter (1μm, made by Whatman Inc.), and was concentrated by Dry Thermo-unit PTU-1C. The residue was purified by preparative HPLC made by Gilson Inc. (PLRP-S column 5 μm 100 A, 50 x 25 mm, 40% to 100% aqueous solution of acetonitrile). The resulting compound was analyzed by LC MASS made by Gilson Inc. (Shiseido capsule pack C18 2 x 5 cm, λ = 220 nm, temperature 40°C, A luquid 0.05% trifluoroacetic acid solution: B liquid acetonitrile: 10 to 95% B liquid (for 4 minutes) 95% B liquid (for 1.5 minutes), electrospray ionization mass spectrum).

Example 97

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-butyl benzamide

[0311] 20.6 mg
LC-MS: purity 99%, Rt = 3.84 mjn, m/z: 494 $[M+H]^+$

Example 98

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(cyclohexylmethyl)benzamide

[0312] 23.6 mg
LC-MS: purity 96%, Rt = 4.15 mjn, m/z: 534 $[M+H]^+$

Example 99

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-cyclopropyl benzamide

[0313] 22.4 mg
^{1}H-NMR ($CDCl_3$) δ; 0.07 to 0.15 (2H, m), 0.56 to 0.65 (2H, m), 2.78 to 2.87 (2H, m), 6.22 (1H, s), 6.74 (1H, d, J = 9.2 Hz), 6.93 (1H, t, J = 7.4 Hz), 7.17 to 7.40 (14H, m), 7.70 (1H, d, J = 2.8 Hz), 7.93 (1H, dd, J = 2.8, 8.8 Hz), 8.00 (1H, s), 8.09 (1H, bs), 8.28 (1H, s)
LC-MS: purity 99%, Rt = 3.55 mjn, m/z: 478 $[M+H]^+$

Example 100

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(1,3-benzodioxol-5-ylmethylcyclohexylmethyl)benzamide

[0314] 26.5 mg
LC-MS: purity 98%, Rt = 3.69 mjn, m/z: 572 $[M+H]^+$

Example 101

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-phenylethyl)benzamide

[0315] 26.1 mg
LC-MS: purity 99%, Rt = 3.89 mjn, m/z: 542 $[M+H]^+$

Example 102

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(3-phenylpropyl)benzamide

[0316] 27.0 mg
LC-MS: purity 99%, Rt = 4.00 mjn, m/z: 556 $[M+H]^+$

Example 103

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(benzhydryl)benzamide

[0317] 30.7 mg
LC-MS: purity 99%, Rt = 4.13 mjn, m/z: 604 $[M+H]^+$

Example 104

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-methoxyethyl)benzamide

[0318] 25.7 mg
LC-MS: purity 98%, Rt = 3.46 mjn, m/z: 496 $[M+H]^+$

Example 105

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(3-methylthiopropyl)benzamide

[0319] 26.4 mg
LC-MS: purity 99%, Rt = 3.71 mjn, m/z: 526 $[M+H]^+$

Example 106

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(tetrahydrofuran-2-ylmethyl)benzamide

[0320] 26.3 mg
LC-MS: purity 99%, Rt = 3.56 mjn, m/z: 522 $[M+H]^+$

Example 107

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[2-(1H-indol-3-yl)ethyl]benzamide

[0321] 27.9 mg
LC-MS: purity 99%, Rt = 3.74 mjn, m/z: 581 $[M+H]^+$

Example 108

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(1-ethylpropyl)benzamide

[0322] 26.7 mg
LC-MS: purity 97%, Rt = 3.93 mjn, m/z: 508 $[M+H]^+$

Example 109

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-cyclohexyl benzamide (24)

[0323] 24.9 mg
LC-MS: purity 99%, Rt = 4.00 mjn, m/z: 520 $[M+H]^+$

Example 110

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-ethynyl benzamide (25)

[0324] 24.1 mg
LC-MS: purity 100%, Rt = 3.50 mjn, m/z: 476 $[M+H]^+$

Example 111

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(4-trifluoromethylbenzyl)benzamide

[0325] 24.3 mg
^{1}H-NMR ($CDCl_3$) δ; 4.51 (2H, d, J = 5.6 Hz), 6.29 (1H, s), 6.87 (1H, d, J = 9.2 Hz), 7.03 to 7.44 (19H, m), 7.55 (1H, s), 7.72 (1H, s), 7.83 (1H, d, J = 3.0 Hz), 7.92 (1H, dd, J = 3.0, 8.4 Hz), 8.63 (1H, t, J = 5.6 Hz)
LC-MS: purity 99%, Rt = 4.02 mjn, m/z: 596 $[M+H]^+$

Example 112

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[2-(3,4-dimethoxyphenyl)ethyl]benzamide

[0326] 29.5 mg
LC-MS: purity 99%, Rt = 3.67 mjn, m/z: 602 $[M+H]^+$

Example 113

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(3,3-diphenylpropyl)benzamide

[0327] 24.7 mg
LC-MS: purity 99%, Rt = 4.22 mjn, m/z: 632 $[M+H]^+$

Example 114

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2,3-dihydro-1H-indene-2-yl)benzamide

[0328] 27.4 mg
LC-MS: purity 99%, Rt = 3.96 mjn, m/z: 554 $[M+H]^+$

Example 115

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(3-isopropoxypropyl)benzamide

[0329] 27.4 mg
LC-MS: purity 99%, Rt = 3.75 mjn, m/z: 538 $[M+H]^+$

Example 116

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-oxoazepan-3-yl)benzamide

[0330] 29.0 mg
LC-MS: purity 99%, Rt = 3.30 mjn, m/z: 549 $[M+H]^+$

Example 117

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-furylmethyl)benzamide

[0331] 24.6 mg
LC-MS: purity 99%, Rt = 3.65 mjn, m/z: 518 $[M+H]^+$

Example 118

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[3-(2-oxopyrrolidin-1-yl)propyl]benzamide

[0332] 16.3 mg
LC-MS: purity 99%, Rt = 3.22 mjn, m/z: 563 $[M+H]^+$

Example 119

N-[3-(Azocan-1-ylcarbonyl)-4-(benzhydryloxy)phenyl]-N'-phenylurea

[0333] 20.1 mg
LC-MS: purity 99%, Rt = 3.89 mjn, m/z: 534 $[M+H]^+$

Example 120

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[2-(dimethylamino)ethyl]benzamide

[0334] 22.5 mg
LC-MS: purity 99%, Rt = 2.62 mjn, m/z: 508 $[M+H]^+$

Example 121

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[3-(diethylamino)propyl]benzamide

[0335] 21.1 mg
LC-MS: purity 98%, Rt = 2.72 mjn, m/z: 551 $[M+H]^+$

Example 122

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-piperidin-1-ylethyl)benzamide

[0336] 24.4 mg
LC-MS: purity 99%, Rt = 2.73 mjn, m/z: 549 $[M+H]^+$

Example 123

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-morpholin-4-ylethyl)benzamide

[0337] 24.4 mg
LC-MS: purity 99%, Rt = 2.63 mjn, m/z: 551 $[M+H]^+$

Example 124

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[3-(4-methylpiperidin-1-yl)propyl]benzamide

[0338] 26.4 mg
LC-MS: purity 98%, Rt = 2.39 mjn, m/z: 578 $[M+H]^+$

Example 125

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-{3-[methyl(phenyl)amino]propyl)benzamide

[0339] 27.5 mg
LC-MS: purity 96%, Rt = 3.06 mjn, m/z: 585 $[M+H]^+$

Example 126

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(1-benzylpiperidin-4-yl)benzamide

[0340] 25.6 mg
LC-MS: purity 98%, Rt = 2.85 mjn, m/z: 611 $[M+H]^+$

Example 127

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2,2,6,6-tetramethylpiperidin-4-yl)benzamide

[0341] 25.7 mg
LC-MS: purity 100%, Rt = 2.74 mjn, m/z: 577 $[M+H]^+$

Example 128

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-anilin oethyl)benzamide

[0342] 20.4 mg
LC-MS: purity 98%, Rt = 3.49 mjn, m/z: 557 $[M+H]^+$

Example 129

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(pyridin-2-ylmethyl)benzamide

[0343] 23.8 mg
LC-MS: purity 98%, Rt = 2.79 mjn, m/z: 529 $[M+H]^+$

Example 130

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-pyridin-4-ylethyl)benzamide

[0344] 26.1 mg
LC-MS: purity 98%, Rt = 2.64 mjn, m/z: 543 $[M+H]^+$

Example 131

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[3-(1H-imidazol-1-yl)propyl]benzamide

[0345] 27.2 mg
LC-MS: purity 99%, Rt = 2.64 mjn, m/z: 546 $[M+H]^+$

Example 132

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[2-(diisopropylamino)ethyl]benzamide

[0346] 26.1 mg
LC-MS: purity 97%, Rt = 2.83 mjn, m/z: 565 $[M+H]^+$

Example 133

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[3-(dimethylamino)-2,2-dimethylpropyl]benzamide

[0347] 19.7 mg
LC-MS: purity 98%, Rt = 2.78 mjn, m/z: 551 $[M+H]^+$

Example 134

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-[3-(2-methylpiperidin-1-yl)propyl]benzamide

[0348] 23.9 mg
LC-MS: purity 98%, Rt = 2.78 mjn, m/z: 577 $[M+H]^+$

Example 135

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(2-pyrrolidin-1-ylethyl)benzamide

[0349] 21.7 mg
LC-MS: purity 95%, Rt = 2.67 mjn, m/z: 535 $[M+H]^+$

Example 136

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-{2-[ethyl(3-methylphenyl)amino]ethyl}benzamide

[0350] 26.9 mg
LC-MS: purity 98%, Rt = 3.27 mjn, m/z: 599 $[M+H]^+$

Example 137

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(1-benzylpyrrolidin-3-yl)benzamide

[0351] 23.7 mg
LC-MS: purity 96%, Rt = 2.88 mjn, m/z: 597 $[M+H]^+$

Example 138

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-{3-[bis(2-hydroxyethyl)amino]propyl}benzamide

[0352] 25.0 mg
LC-MS: purity 97%, Rt = 2.57 mjn, m/z: 583 $[M+H]^+$

Example 139

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-{2-[(5-nitropyridyl-2-yl)amino]ethyl}benzamide (54)

[0353] 11.1 mg
LC-MS: purity 95%, Rt = 3.54 mjn, m/z: 603 $[M+H]^+$

Example 140

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(pyridin-4-ylmethyl)benzamide (55)

[0354] 26.2 mg
LC-MS: purity 99%, Rt = 2.63 mjn, m/z: 529 $[M+H]^+$

Example 141

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(pyridin-3-ylmethyl)benzamide

[0355] 27.1 mg
LC-MS: purity 99%, Rt = 2.66 mjn, m/z: 529 $[M+H]^+$

Example 142

5-(Anilinocarbonylamino)-2-benzhydryloxy-N-(pyridin-3-ylethyl)benzamide

[0356] 25.3 mg
LC-MS: purity 99%, Rt = 2.66 mjn, m/z: 543 $[M+H]^+$

Example 143

N-[4-(Benzhydryloxy)-3-(octahydroquinolin-1 (2H)-ylcarbonyl)phenyl]-N'-phenylurea

[0357] 16.1 mg
LC-MS: purity 95%, Rt = 4.10 mjn, m/z: 560 $[M+H]^+$

Combinatorial synthesis

[0358] The compounds of Examples 144 to 227 were synthesized according to the followings.

[0359] To a solution (1 mL) of methyl 5-amino-2-benzhydryloxy benzoate (0.900 mmol), diisopropylethyl amine (0.108 mmol) in acetonitrile was added N,N-disuccinimidyl carbamate (0.108 mmol) at 0°C, and the mixture was stirred at 0°C for 40 minutes. This solution was added to diisopropylethyl amine (0.108 mmol), amine (0.09 mmol), and the mixture was stirred for 12 hours at room temperature. The solvent was evaporated by Dry Thermo-unit, to the residue were added water and dichloromethane, and the layer of dichloromethane was separated by PTFE filter (1 μm pore size, Whatman Inc.). Dichloromethane was evaporated by Dry Thermo-unit, and the residue was purified by preparative

HPLC (PLRP-S column 5 μm 100 A, 50 x 25 mm, 40% to 100% aqueous solution of acetonitrile). The resulting compound was analyzed by LC MASS made by Gilson Inc. (Shiseido capsule pack C18 2 x 5 cm, λ = 220 nm, temperature 40°C, A solution 0.05% trifluoroacetic acid solution: B liquid acetonitrile: 10 to 95% B liquid (for 4 minutes) 95% B liquid (for 1.5 minutes), electrospray ionization mass spectrum).

Example 144

Methyl 2-(benzhydryloxy)-5-[({[2-(dimethylamino)ethyl]amino}carbonyl)amino]benzoate

[0360] 18.3 mg, LC-MS: purity 98%, Rt = 2.57 mjn, m/z: 448 $[M+H]^+$

Example 145

Methyl 2-(benzhydryloxy)-5-[({[3-(diethylamino)propyl]amino}carbonyl)amino]benzoate

[0361] 19.8 mg, LC-MS: purity 96%, Rt = 2.66 mjn, m/z: 490 $[M+H]^+$

Example 146

Methyl 2-(benzhydryloxy)-5-({[(2-piperazin-1-ylethyl)amino]carbonyl}amino)benzoate

[0362] 19.5 mg, LC-MS: purity 96%, Rt = 2.69 mjn, m/z: 488 $[M+H]^+$

Example 147

Methyl 2-(benzhydryloxy)-5-({[(2-morpholin-4-ylethyl)amino]carbonyl}amino)benzoate

[0363] 18.3 mg
^{1}H-NMR ($CDCl_3$) δ; 2.41 - 2.51 (6H, m), 3.26 to 3.35 (2H, m), 3.61 to 3.65 (4H, m), 3.90 (3H, s), 5.17 (1H, bs), 6.25 (1H, s), 6.85 to 6.89 (2H, m), 7.20 to 7.53 (12H, m), 7.67 (1H, d, J = 2.6 Hz)
LC-MS: purity 100%, Rt = 2.59 mjn, m/z: 490 $[M+H]^+$

Example 148

Methyl 2-(benzhydryloxy)-5-[({[3-(4-methylpiperazin-1-yl)propyl]amino}carbonyl)amino]benzoate

[0364] 22.1 mg
LC-MS: purity 98%, Rt = 2.33 mjn, m/z: 517 $[M+H]^+$

Example 149

Methyl 2-(benzhydryloxy)-5-{[({3-[methyl(phenyl)amino]propyl}amino)carbonyl]amino}benzoate

[0365] 25.9 mg, LC-MS: purity 98%, Rt = 2.85 mjn, m/z: 524 $[M+H]^+$

Example 150

Methyl 2-(benzhydryloxy)-5-({[(1-benzylpiperidin-4-yl)amino]carbonyl}amino)benzoate

[0366] 24.7 mg, LC-MS: purity 99%, Rt = 2.80 mjn, m/z: 550 $[M+H]^+$

Example 151

Methyl 2-(benzhydryloxy)-5-({[(2,2,6,6-tetramethylpiperidin-4-yl)amino]carbonyl}amino)benzoate

[0367] 12.6 mg, LC-MS: purity 99%, Rt = 2.72 mjn, m/z: 516 $[M+H]^+$

Example 152

Methyl 2-(benzhydryloxy)-5-({[(2-anilin oethyl)amino]carbonyl}amino)benzoate

[0368] 25.5 mg, LC-MS: purity 98%, Rt = 3.01 mjn, m/z: 496 $[M+H]^+$

Example 153

Methyl 2-(benzhydryloxy)-5-({[(piperidin-2-ylmethyl)amino]carbonyl}amino)benzoate

[0369] 16.8 mg, LC-MS: purity 98%, Rt = 2.61 mjn, m/z: 468 $[M+H]^+$

Example 154

Methyl 2-(benzhydryloxy)-5-({[(2-pyridin-4-ylethyl)amino]carbonyl}amino)benzoate

[0370] 17.1 mg, LC-MS: purity 95%, Rt = 2.58 mjn, m/z: 482 $[M+H]^+$

Example 155

Methyl 2-(benzhydryloxy)-5-[({[3-(1H-imidazol-1-yl)propyl]amino}carbonyl)amino]benzoate

[0371] 13.5 mg
^{1}H-NMR ($CDCl_3$) δ; 1.94 to 2.04 (2H, m), 3.12 to 3.21 (2H, m), 3.88 (3H, s), 3.99 (2H, t, J = 7.0 Hz), 5.31 (1H, bs), 6.23 (1H, s), 6.84 (1H, d, J = 8.8 Hz), 6.92 to 7.52 (15H, m), 7.63 (1H, d, J = 2.6 Hz)
LC-MS: purity 100%, Rt = 2.59 mjn, m/z: 485 $[M+H]^+$

Example 156

Methyl 2-(benzhydryloxy)-5-[({[2-(diisopropylamino)ethyl]amino}carbonyl)amino]benzoate

[0372] 18.7 mg, LC-MS: purity 100%, Rt = 2.80 mjn, m/z: 504 $[M+H]^+$

Example 157

Methyl 2-(benzhydryloxy)-5-[({[3-(dimethylamino)-2,2-dimethylpropyl]amino}carbonyl)amino]benzoate

[0373] 22.4 mg, LC-MS: purity 98%, Rt = 2.68 mjn, m/z: 490 $[M+H]^+$

Example 158

Methyl 2-(benzhydryloxy)-5-[({[3-(2-methylpiperidin-1-yl)propyl]amino}carbonyl)amino]benzoate

[0374] 21.0 mg, LC-MS: purity 996%, Rt = 2.73 mjn, m/z: 516 $[M+H]^+$

Example 159

Methyl 2-(benzhydryloxy)-5-({[(3-morpholin-4-ylpropyl)amino]carbonyl}amino)benzoate

[0375] 23.7 mg, LC-MS: purity 96%, Rt = 2.60 mjn, m/z: 504 $[M+H]^+$

Example 160

Methyl 2-(benzhydryloxy)-5-({[(2-pyrrolidin-1-ylethyl)amino]carbonyl}amino)benzoate

[0376] 17.1 mg, LC-MS: purity 99%, Rt = 2.62 mjn, m/z: 474 $[M+H]^+$

Example 161

Methyl 2-(benzhydryloxy)-5-{[({2-[ethyl(3-methylphenyl)amino]ethyl}amino)carbonyl]amino}benzoate

[0377] 27.9 mg, LC-MS: purity 98%, Rt = 2.98 mjn, m/z: 538 $[M+H]^+$

Example 162

Methyl 2-(benzhydryloxy)-5-({[(1-benzylpyrrolidin-3-yl)amino]carbonyl}amino)benzoate

[0378] 26.5 mg, LC-MS: purity 97%, Rt = 2.85 mjn, m/z: 536 $[M+H]^+$

Example 163

Methyl 2-(benzhydryloxy)-5-[({[2-(5-nitropyridin-2-yl)ethyl]amino}carbonyl)amino]benzoate

[0379] 25.1 mg, LC-MS: purity 96%, Rt = 3.35 mjn, m/z: 542 $[M+H]^+$

Example 164

Methyl 2-(benzhydryloxy)-5-({[(pyridin-4-ylmethyl)amino]carbonyl}amino)benzoate (21)

[0380] 21.5 mg, LC-MS: purity 99%, Rt = 2.58 mjn, m/z: 468 $[M+H]^+$

Example 165

Methyl 2-(benzhydryloxy)-5-({[(pyridin-3-ylmethyl)amino]carbonyl}amino)benzoate

[0381] 22.5 mg, LC-MS: purity 100%, Rt = 2.58 mjn, m/z: 468 $[M+H]^+$

Example 166

Methyl 2-(benzhydryloxy)-5-[({[2-(3-pyridin yl)ethyl]amino}carbonyl)amino]benzoate

[0382] 20.4 mg, LC-MS: purity 99%, Rt = 2.59 mjn, m/z: 482 $[M+H]^+$

Example 167

Methyl 2-(benzhydryloxy)-5-({[[2-(dimethylamino)ethyl](methyl)amino]carbonyl}amino)benzoate

[0383] 18.0 mg, LC-MS: purity 99%, Rt = 2.58 mjn, m/z: 462 $[M+H]^+$

Example 168

Methyl 2-(benzhydryloxy)-5-({[(1-benzylpyrrolidin-3-yl)amino]carbonyl}amino)benzoate

[0384] 24.1 mg, LC-MS: purity 86%, Rt = 2.92 mjn, m/z: 550 $[M+H]^+$

Example 169

Methyl 2-(benzhydryloxy)-5-({(ethyl(pyridin-4-ylmethyl)amino]carbonyl}amino)benzoate

[0385] 25.2 mg
^{1}H-NMR ($CDCl_3$) δ; 1.21 (3H, t, J = 7.4 Hz), 3.35 (2H, q, J = 7.4 Hz), 3.90 (3H, s), 4.55 (2H, s), 6.25 (2H, bs), 6.84 (1H, d, J = 9.2 Hz), 7.19 to 7.53 (13H, m), 7.64 (1H, d, J = 3.2 Hz), 8.56 (2H, d, J = 5.8 Hz)
LC-MS: purity 98%, Rt = 2.66 mjn, m/z: 496 $[M+H]^+$

Example 170

Methyl 2-(benzhydryloxy)-5-({[bis(pyridin-3-ylmethyl)amino]carbonyl}amino)benzoate

[0386] 28.1 mg, LC-MS: purity 98%, Rt = 2.31 mjn, m/z: 559 $[M+H]^+$

Example 171

Methyl 2-(benzhydryloxy)-5-{[(4-ethylpiperazin-1-yl)carbonyl]amino}benzoate

[0387] 26.1 mg, LC-MS: purity 98%, Rt = 2.58 mjn, m/z: 474 $[M+H]^+$

Example 172

Methyl 2-(benzhydryloxy)-5-({[4-(2-ethoxy-2-oxoethyl)piperazin-1-yl]carbonyl}amino)benzoate

[0388] 22.8 mg, LC-MS: purity 99%, Rt = 2.67 mjn, m/z: 532 $[M+H]^+$

Example 173

Methyl 2-(benzhydryloxy)-5-{[(4-benzylpiperazin-1-yl)carbonyl]amino}benzoate

[0389] 25.3 mg, LC-MS: purity 99%, Rt = 2.77 mjn, m/z: 536 $[M+H]^+$

Example 174

Methyl 2-(benzhydryloxy)-5-{[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]amino}benzoate

[0390] 28.7 mg, LC-MS: purity 100%, Rt = 2.66 mjn, m/z: 523 $[M+H]^+$

Example 175

Methyl 2-(benzhydryloxy)-5-{[(4-benzhydrylpiperazin-1-yl)carbonyl]amino}benzoate

[0391] 27.4 mg, LC-MS: purity 98%, Rt = 3.03 mjn, m/z: 612 $[M+H]^+$

Example 176

Methyl 2-(benzhydryloxy)-5-{[(4-phenylpiperazin-1-yl)carbonyl]amino}benzoate

[0392] 28.6 mg, LC-MS: purity 99%, Rt = 3.43 mjn, m/z: 522 $[M+H]^+$

Example 177

Methyl 2-(benzhydryloxy)-5-({[4-(2-methoxyphenyl)piperazin-1-yl]carbonyl}amino)benzoate

[0393] 28.8 mg, LC-MS: purity 99%, Rt = 3.12 mjn, m/z: 552 $[M+H]^+$

Example 178

Methyl 2-(benzhydryloxy)-5-[(1,4'-bipiperidin-1-ylcarbonyl)amino]benzoate

[0394] 16.8 mg, LC-MS: purity 100%, Rt = 2.66 mjn, m/z: 528 $[M+H]^+$

Example 179

Methyl 2-(benzhydryloxy)-5-({[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}amino)benzoate

[0395] 18.9 mg, LC-MS: purity 99%, Rt = 2.61 mjn, m/z: 474 $[M+H]^+$

Example 180

Methyl 2-(benzhydryloxy)-5-({[benzyl(1-benzylpyrrolidin-3-yl)amino]carbonyl}amino)benzoate

[0396] 26.6 mg, LC-MS: purity 98%, Rt = 3.19 mjn, m/z: 626 $[M+H]^+$

Example 181

Methyl 2-(benzhydryloxy)-5-({[bis(2-pyridin ylmethyl)amino]carbonyl}amino)benzoate

[0397] 23.4 mg, LC-MS: purity 99%, Rt = 2.72 mjn, m/z: 559 $[M+H]^+$

Example 182

Methyl 2-(benzhydryloxy)-5-{[(4-methyl-1,4-diazepin-1-yl)carbonyl]amino}benzoate

[0398] 21.7 mg, LC-MS: purity 99%, Rt = 2.55 mjn, m/z: 474 $[M+H]^+$

Example 183

Methyl 2-(benzhydryloxy)-5-({[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}amino)benzoate

[0399] 24.6 mg, LC-MS: purity 99%, Rt = 2.52 mjn, m/z: 490 $[M+H]^+$

Example 184

Methyl 2-(benzhydryloxy)-5-({[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}amino)benzoate

[0400] 25.4 mg, LC-MS: purity 98%, Rt = 2.78 mjn, m/z: 580 $[M+H]^+$

Example 185

Methyl 2-(benzhydryloxy)-5-{[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]amino}benzoate

[0401] 27.1 mg, LC-MS: purity 99%, Rt = 2.90 mjn, m/z: 562 $[M+H]^+$

Example 186

Methyl 2-(benzhydryloxy)-5-[({4-[(2E)-3-phenylpropen-2-yl]piperazin-1-yl}carbonyl)amino]benzoate

[0402] 25.1 mg, LC-MS: purity 99%, Rt = 2.67 mjn, m/z: 532 $[M+H]^+$

Example 187

Methyl 2-(benzhydryloxy)-5-[({benzyl[2-(dimethylamino)ethyl]amino}carbonyl)amino]benzoate

[0403] 22.3 mg, LC-MS: purity 99%, Rt = 2.89 mjn, m/z: 538 $[M+H]^+$

Example 188

Methyl 2-(benzhydryloxy)-5-({[methyl(1-methylpiperidin-4-yl)amino]carbonyl}amino)benzoate

[0404] 19.2 mg, LC-MS: purity 98%, Rt = 2.60 mjn, m/z: 488 $[M+H]^+$

Example 189

Methyl 2-(benzhydryloxy)-5-({[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}amino)benzoate

[0405] 8.1 mg, LC-MS: purity 93%, Rt = 2.77 mjn, m/z: 514 $[M+H]^+$

Example 190

Methyl 2-(benzhydryloxy)-5-{[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]amino}benzoate

[0406] 20.2 mg, LC-MS: purity 97%, Rt = 2.61 mjn, m/z: 514 $[M+H]^+$

Example 191

Methyl 2-(benzhydryloxy)-5-({[(4-cyclohexylphenyl)amino]carbonyl}amino)benzoate

[0407] 21.6 mg, LC-MS: purity 99%, Rt = 4.36 mjn, m/z: 535 $[M+H]^+$

Example 192

Methyl 2-(benzhydryloxy)-5-{[(pyridin-2-ylamino)carbonyl]amino}benzoate

[0408] 17.1 mg, LC-MS: purity 95%, Rt = 2.98 mjn, m/z: 454 $[M+H]^+$

Example 193

Methyl 2-(benzhydryloxy)-5-({[(5-methylisoxazol-3-yl)amino]carbonyl}amino)benzoate

[0409] 10.4 mg, LC-MS: purity 95%, Rt = 3.49 mjn, m/z: 461 $[M+H]^+$

Example 194

Methyl 2-(benzhydryloxy)-5-({[(4-methylphenyl)amino]carbonyl}amino)benzoate

[0410] 21.1 mg, LC-MS: purity 100%, Rt = 3.78 mjn, m/z: 489 $[M+Na]^+$

Example 195

Methyl 2-(benzhydryloxy)-5-({[(4-hydroxyphenyl)amino]carbonyl}amino)benzoate

[0411] 21.5 mg, LC-MS: purity 96%, Rt = 3.27 mjn, m/z: 491 $[M+Na]^+$

Example 196

Methyl 2-(benzhydryloxy)-5-({[(4-fluorophenyl)amino]carbonyl}amino)benzoate

[0412] 21.3 mg, LC-MS: purity 97%, Rt = 3.69 mjn, m/z: 471 $[M+H]^+$

Example 197

Methyl 2-(benzhydryloxy)-5-({[(2-fluorophenyl)amino]carbonyl}amino)benzoate

[0413] 16.5 mg, LC-MS: purity 98%, Rt = 3.75 mjn, m/z: 493 $[M+Na]^+$

Example 198

Methyl 2-(benzhydryloxy)-5-({[(3-cyanophenyl)amino]carbonyl}amino)benzoate

[0414] 18.2 mg, LC-MS: purity 84%, Rt = 3.75 mjn, m/z: 500 $[M+Na]^+$

Example 199

Methyl 2-(benzhydryloxy)-5-({[(4-cyanophenyl)amino]carbonyl}amino)benzoate

[0415] 11.2 mg, LC-MS: purity 85%, Rt = 3.64 mjn, m/z: 500 $[M+Na]^+$

Example 200

Methyl 2-(benzhydryloxy)-5-({[(3,5-dimethylphenyl)amino]carbonyl}amino)benzoate

[0416] 23.8 mg, LC-MS: purity 94%, Rt = 3.92 mjn, m/z: 481 $[M+H]^+$

Example 201

Methyl 2-(benzhydryloxy)-5-({[(4-ethylphenyl)amino]carbonyl}amino)benzoate

[0417] 23.8 mg, LC-MS: purity 96%, Rt = 3.92 mjn, m/z: 503 $[M+H]^+$

Example 202

Methyl 2-(benzhydryloxy)-5-({[(3-fluoro-4-methylphenyl)amino]carbonyl}amino)benzoate

[0418] 24.2 mg, LC-MS: purity 99%, Rt = 3.87 mjn, m/z: 507 $[M+Na]^+$

Example 203

Methyl 2-(benzhydryloxy)-5-({[(2-fluoro-4-methylphenyl)amino]carbonyl}amino)benzoate

[0419] 21.7 mg, LC-MS: purity 99%, Rt = 3.87 mjn, m/z: 507 $[M+Na]^+$

Example 204

Methyl 2-(benzhydryloxy)-5-({[(4-chlorophenyl)amino]carbonyl}amino)benzoate

[0420] 25.4 mg, LC-MS: purity 100%, Rt = 3.88 mjn, m/z: 509 $[M+Na]^+$

Example 205

Methyl 2-(benzhydryloxy)-5-({[(3-chlorophenyl)amino]carbonyl}amino)benzoate

[0421] 22.7 mg, LC-MS: purity 98%, Rt = 3.91 mjn, m/z: 509 $[M+Na]^+$

Example 206

Methyl 2-(benzhydryloxy)-5-({[(2,4-difluorophenyl)amino]carbonyl}amino)benzoate

[0422] 20.2 mg, LC-MS: purity 94%, Rt = 3.78 mjn, m/z: 511 $[M+Na]^+$

Example 207

Methyl 2-(benzhydryloxy)-5-({[(3,4-difluorophenyl)amino]carbonyl}amino)benzoate

[0423] 19.7 mg, LC-MS: purity 98%, Rt = 3.828 mjn, m/z: 511 $[M+Na]^+$

Example 208

Methyl 2-(benzhydryloxy)-5-{[(1H-indol-5-ylamino)carbonyl]amino}benzoate

[0424] 17.3 mg, LC-MS: purity 97%, Rt = 3.47 mjn, m/z: 492 $[M+H]^+$

Example 209

Methyl 2-(benzhydryloxy)-5-{[(2,3-dihydro-1H-indene-5-ylamino)carbonyl]amino}benzoate

[0425] 29.4 mg, LC-MS: purity 91%, Rt = 3.95 mjn, m/z: 493 $[M+Na]^+$

Example 210

Methyl 2-(benzhydryloxy)-5-({[(4-acetylphenyl)amino]carbonyl}amino)benzoate

[0426] 19.5 mg, LC-MS: purity 100%, Rt = 3.55 mjn, m/z: 517 $[M+Na]^+$

Example 211

Methyl 2-(benzhydryloxy)-5-({[(4-isopropylphenyl)amino]carbonyl}amino)benzoate

[0427] 22.6 mg, LC-MS: purity 94%, Rt = 3.95 mjn, m/z: 517 $[M+Na]^+$

Example 212

Methyl 2-(benzhydryloxy)-5-({[(2-propylphenyl)amino]carbonyl}amino)benzoate

[0428] 25.6 mg, LC-MS: purity 95%, Rt = 3.95 mjn, m/z: 495 $[M+H]^+$

Example 213

Methyl 2-(benzhydryloxy)-5-[({[4-(dimethylamino)phenyl]amino}carbonyl)amino]benzoate

[0429] 22.3 mg, LC-MS: purity 95%, Rt = 2.77 mjn, m/z: 496 $[M+H]^+$

Example 214

Methyl 2-(benzhydryloxy)-5-({[(2-methoxy-5-methylphenyl)amino]carbonyl}amino)benzoate

[0430] 25.6 mg, LC-MS: purity 98%, Rt = 3.91 mjn, m/z: 497 $[M+H]^+$

Example 215

Methyl 2-(benzhydryloxy)-5-({[(4-ethoxyphenyl)amino]carbonyl}amino)benzoate

[0431] 24.9 mg, LC-MS: purity 99%, Rt = 3.91 mjn, m/z: 497 $[M+H]^+$

Example 216

Methyl 2-(benzhydryloxy)-5-({[(4-nitrophenyl)amino]carbonyl}amino)benzoate

[0432] 7.6 mg, LC-MS: purity 86%, Rt = 3.77 mjn, m/z: 520 $[M+Na]^+$

Example 217

Methyl 2-(benzhydryloxy)-5-({[(3-methylthiophenyl)amino]carbonyl}amino)benzoate

[0433] 24.8 mg, LC-MS: purity 99%, Rt = 3.83 mjn, m/z: 499 $[M+H]^+$

Example 218

Methyl 2-(benzhydryloxy)-5-({[(3-chloro-4-methylphenyl)amino]carbonyl}amino)benzoate

[0434] 26.6 mg, LC-MS: purity 93%, Rt = 4.02 mjn, m/z: 501 $[M+H]^+$

Example 219

Methyl 2-(benzhydryloxy)-5-{[(1-naphthylamino)carbonyl]amino}benzoate

[0435] ^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 6.20 (1H, s), 6.52 (1H, s), 6.70 (1H, s), 6.80 (1H, d, J = 9.2 Hz), 7.18 to 8.00 (19H, m)
22.6 mg, LC-MS: purity 98%, Rt = 3.58 mjn, m/z: 525 $[M+Na]^+$

Example 220

Methyl 2-(benzhydryloxy)-5-{[(quinolin-6-ylamino)carbonyl]amino}benzoate

[0436] 24.0 mg, LC-MS: purity 97%, Rt = 2.80 mjn, m/z: 504 $[M+H]^+$

Example 221

Methyl 2-(benzhydryloxy)-5-{[(isoquinolin-5-ylamino)carbonyl]amino}benzoate

[0437] 20.1 mg, LC-MS: purity 99%, Rt = 2.76 mjn, m/z: 504 $[M+H]^+$

Example 222

Methyl 2-(benzhydryloxy)-5-({[(3-chloro-4-fluorophenyl)amino]carbonyl}amino)benzoate

[0438] 23.0 mg, LC-MS: purity 98%, Rt = 3.92 mjn, m/z: 527 $[M+Na]^+$

Example 223

Methyl 2-(benzhydryloxy)-5-({[(1-oxo-2,3-dihydro-1H-indane-5-yl)amino]carbonyl}amino)benzoate

[0439] 11.4 mg
^{1}H-NMR ($CDCl_3$) δ; 2.66 (2H, t, J = 7.0 Hz), 3.06 (2H, t, J = 7.6Hz), 3.91 (3H, s), 6.23 (1H, s), 6.89 to 7.38 (18H, m)
LC-MS: purity 97%, Rt = 3.50 mjn, m/z: 529 $[M+Na]^+$

Example 224

Methyl 2-(benzhydryloxy)-5-({[(4-tert-butylphenyl)amino]carbonyl}amino)benzoate

[0440] 27.7 mg, LC-MS: purity 100%, Rt = 4.13 mjn, m/z: 509 $[M+H]^+$

Example 225

Methyl 2-(benzhydryloxy)-5-({[(2-tert-butylphenyl)amino]carbonyl}amino)benzoate

[0441] 19.6 mg

^{1}H-NMR ($CDCl_3$) δ; 1.36 (9H, s), 3.88 (3H, s), 6.11 (1H, s), 6.20 (1H, s), 6.24 (1H, s), 6.85 (1H, d, J = 8.4 Hz), 7.22 to 7.55 (16H, m)

LC-MS: purity 98%, Rt = 3.91 mjn, m/z: 509 $[M+H]^+$

Example 226

Methyl 2-(benzhydryloxy)-5-{[({3-[(methylamino)carbonyl]phenyl}amino)carbonyl]amino}benzoate

[0442] 2.6 mg, LC-MS: purity 92%, Rt = 3.25 mjn, m/z: 510 $[M+H]^+$

Example 227

Methyl 2-(benzhydryloxy)-5-[({[4-(acetylamino)phenyl]amino}carbonyl)amino]benzoate

[0443] 1.6 mg, LC-MS: purity 86%, Rt = 3.23 mjn, m/z: 510 $[M+H]^+$

Example 228

Methyl 5-(anilinocarbonylamino)-2-benzyloxy benzoate

(1) Methyl 2-benzyloxy-5-nitrobenzoate

[0444] To a solution (60 mL) of methyl 2-hydroxy-5-nitrobenzoate (3.94 g, 20.0 mmol) in DMF was added sodium hydride (60%, 0.96 g, 24.0 mmol) under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. To the reaction solution was added benzyl bromide (2.85 mL, 24.0 mmol), the mixture was stirred at 70°C for 3 hours, poured into an ice-cooled aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water and saturated brine, and was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 3:1) to obtain crystals, which were filtrated and were washed with ethyl acetate and hexane. 4.41 g (77%)

^{1}H-NMR ($CDCl_3$) δ; 3.95 (3H, s), 5.31 (2H, s), 7.10 (1H, d, J = 9.2 Hz), 7.26 to 7.50 (5H, m), 8.32 (1H, dd, J = 9.2, 3.0 Hz), 8.74 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-benzyloxy benzoate

[0445] A mixed solution of methyl 2-benzyloxy-5-nitrobenzoate (2.88 g, 10 mmol), 5% iridium carbon (0.71 g) and ethyl acetate (30 mL) was stirred under hydrogen atmosphere for 5 hours. The catalyst was removed, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 3:1), to obtain the titled compound as oil. 1.74 g (67%)

^{1}H-NMR ($CDCl_3$) δ; 3.52 (2H, bs), 3.88 (3H, s), 5.08 (2H, s), 6.77 (1H, dd, J = 8.8, 2.8 Hz), 6.86 (1H, d, J = 8.8 Hz), 7.17 (1H, d, J = 2.8 Hz), 7.28 to 7.50 (5H, m)

(3) Methyl 5-(anilinocarbonylamino)-2-benzyloxy benzoate

[0446] A mixed solution of methyl 5-amino-2-benzyloxy benzoate (2.13 g, 8.3 mmol), phenyl isocyanate (0.99 mL, 9.1 mmol) and THF (50 mL) was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure, and the resulting crude crystals were recrystallized from ethyl acetate and methanol. 2.56 g (82%)

^{1}H-NMR ($CDCl_3$) δ; 3.85 (3H, s), 5.05 (2H, s), 6.89 (1H, d, J = 8.8 Hz), 7.02 to 7.10 (3H, m), 7.16 to 7.52 (10H, m), 7.64 (1H, d, J = 2.6 Hz)

Anal.Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44

Found: C, 70.40; H, 5.29; N, 7.60

Example 229

Methyl 5-[(anilinocarbonyl)amino]-2-phenoxybenzoate

(1) Methyl 5-nitro-2-phenyloxybenzoate

[0447] A mixed solution of methyl 2-chloro-5-nitrobenzoate (1.08 g, 5.0 mmol), phenol (0.47 g, 5.0 mmol), potassium carbonate (0.69 g, 5.0 mmol) and DMF (15 mL) was heated with stirring at 120°C for 1 hour. The reaction solution was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water and saturated brine, and was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting crystal was collected by filtration, and was washed with hexane. 1.12 g (82%)

^{1}H-NMR ($CDCl_3$) δ; 3.94 (3H, s), 6.92 (1H, d, J = 9.0 Hz), 7.07 to 7.12 (2H, m), 7.22 to 7.30 (1H, m), 7.39 to 7.49 (2H, m), 8.24 (1H, dd, J = 9.0, 2.8 Hz), 8.80 (1H, d, J = 2.8 Hz)

(2) Methyl 5-amino-2-phenyloxybenzoate

[0448] A mixed solution of methyl 5-nitro-2-phenyloxybenzoate (0.89 g, 3.3 mmol), 10% palladium carbon (0.24 g) and ethyl acetate (20 mL) was stirred under hydrogen atmosphere for 2 hours. The catalyst was removed, and the solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate and hexane. 0.74 g (94%)

^{1}H-NMR ($CDCl_3$) δ; 3.70 (2H, bd) , 3.73 (3H, s), 6.79 to 7.03 (5H, m), 7.22 to 7.31 (3H, m)

(3) Methyl 5-[(anilinocarbonyl)amino]-2-phenoxybenzoate

[0449] A mixed solution of methyl 5-amino-2-phenyloxybenzoate (0.61 g, 2.5 mmol), phenyl isocyanate (0.30 mL, 2.8 mmol) and THF (15 mL) was stirred at room temperature for 14 hours. The solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate and hexane. 0.86 g (95%)

^{1}H-NMR ($CDCl_3$) δ; 3.74 (3H, s), 6.84 to 6.92 (3H, m), 7.00 to 7.12 (3H, m), 7.19 to 7.30 (7H, m), 7.55 (1H, dd, J = 8.8, 2.6 Hz), 7.76 (1H, d, J = 2.6 Hz)

[0450] The compound of Example 230 was obtained in the same manner as Example 229.

Example 230

Methyl 5-[(anilinocarbonyl)amino]-2-(pyridin-3-yloxy)benzoate

(1) Methyl 5-nitro-2-(pyridin-3-yloxy)benzoate

[0451] ^{1}H-NMR ($CDCl_3$) δ; 3.94 (3H, s), 6.98 (1H, d, J = 9.2 Hz), 7.38 to 7.42 (2H, m), 8.32 (1H, dd, J = 9.2, 2.6 Hz), 8.46 to 8.54 (2H, m), 8.84 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-(pyridin-3-yloxy)benzoate

[0452] 1.66 g (97%)

^{1}H-NMR ($CDCl_3$) δ; 3.73 (3H, s), 3.78 (2H, bs), 6.85 (1H, dd, J = 8.8, 2.8 Hz), 6.92 (1H, d, J = 8.8 Hz), 7.08 to 7.26 (3H, m), 8.26 (1H, dd, J = 4.4, 1.6 Hz), 8.30 (1H, d, J = 2.8 Hz)

(3) Methyl 5-[(anilinocarbonyl)amino]-2-(pyridin-3-yloxy)benzoate

[0453] ^{1}H-NMR ($CDCl_3$) δ; 3.72 (3H, s), 6.95 (1H, d, J = 8.8 Hz), 7.06 to 7.35 (7H, m), 7.43 (1H, s), 7.57 (1H, dd, J = 8.8, 3.0 Hz), 7.61 (1H,s), 7.84 (1H, d, J = 3.0 Hz), 8.24 (1H, d, J = 2.6 Hz), 8.32 (1H, dd, J = 4.4, 1.8 Hz)

Example 231

Methyl 2-[(4-isopropylbenzyl)oxy]-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 2-(4-isopropylbenzyl)oxy-5-nitrobenzoate

[0454] To a solution (150 mL) of methyl 2-hydroxy-5-nitrobenzoate (9.86 g, 50.0 mmol) in DMF was added sodium hydride (60%, 2.40 g, 60.0 mmol) under ice-cooling, the mixture was stirred for 1 hour at room temperature, (4-isopropyl) benzyl bromide (11.9 g, 60.0 mmol) was added to the mixture, and the mixture was stirred at 80°C for 16 hours. The mixture was poured into an ice-cooled aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water and saturated brine, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (toluene) to obtain the titled compound as oil. 5.65 g (34%)

^{1}H-NMR ($CDCl_3$) δ; 1.25 (6H, d, J = 6.8 Hz), 2.85 - 2.99 (1H, m), 3.95 (3H, s), 5.28 (2H, s), 7.11 (1H, d, J = 9.2 Hz), 7.27 (2H, d, J = 8.6 Hz), 7.40 (2H, d, J = 8.6 Hz), 8.32 (1H, dd, J = 9.2, 3.0 Hz), 8.73 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-(4-isopropylbenzyl)oxy benzoate

[0455] A mixed solution of methyl 2-(4-isopropylbenzyl)oxy-5-nitrobenzoate (3.05 g, 9.3 mmol), 5% iridium carbon (0.61 g) and ethyl acetate (40 mL)-methanol (40 mL) was stirred under hydrogen atmosphere for 20 hours. The catalyst was removed, and the filtrate was concentrated and the resulting residue was filtrated. 2.19 g (79%)

^{1}H-NMR ($CDCl_3$) δ; 1.25 (6H,d, J = 7.0 Hz), 2.84 - 2.98 (1H, m), 3.51 (2H, bs), 3.88 (3H, s), 5.04 (2H, s), 6.77 (1H, dd, J = 8.8, 3.0 Hz), 6.88 (1H, d, J = 8.8 Hz), 7.16 (1H, d, J = 3.0 Hz), 7.23 (2H, d, J = 8.2 Hz), 7.39 (2H, d, J = 8.2 Hz)

(3) Methyl 2-[(4-isopropylbenzyl)oxy]-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0456] A mixed solution of methyl 5-amino-2-(4-isopropylbenzyl)oxy benzoate (299 mg, 1.0 mmol), 4-methoxyphenyl isocyanate (143 µl, 1.1 mmol) and THF (10 mL) was stirred at room temperature for 5 hours. The solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate and hexane. 382 mg (85%)

^{1}H-NMR ($CDCl_3$) δ; 1.23 (6H,d, J = 7.0 Hz), 2.82 - 2.97 (1H, m), 3.75 (3H, s), 3.84 (3H, s), 5.03 (2H, s), 6.78 to 6.93 (5H, m), 7.15 to 7.23 (4H, m), 7.36 (2H, d, J = 8.0 Hz), 7.51 (1H, dd, J = 9.0, 2.8 Hz), 7.61 (1H, d, J = 2.8 Hz)

[0457] The following compounds were obtained in the same manner as Example 231.

Example 232

Methyl 2-[(4-isopropylbenzyl)oxy]-5-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0458] ^{1}H-NMR ($CDCl_3$) δ; 1.23 (6H, d, J = 7.0 Hz), 2.81 - 2.95 (1H, m), 3.71 (3H, s), 3.84 (3H, s), 5.01 (2H, s), 6.56 to 6.61 (1H, m), 6.75 to 6.80 (1H, m), 6.90 (1H, d, J = 8.8 Hz), 7.02 (1H, t, J = 2.2 Hz), 7.09 to 7.22 (5H, m), 7.34 (2H, d, J = 8.2 Hz), 7.49 (1H, dd, J = 8.8, 3.0 Hz), 7.62 (1H, d, J = 3.0 Hz)

Example 233

Methyl 2-[(4-isopropylbenzyl)oxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0459] ^{1}H-NMR ($CDCl_3$) δ; 1.23 (6H, d, J = 6.6 Hz), 2.82 - 2.96 (1H, m), 3.82 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 5.05 (2H, s), 6.70 (1H, dd, J = 8.6, 2.0 Hz), 6.77 (1H, d, J = 8.6 Hz), 6.87 (1H, s), 6.93 (1H, d, J = 8.6 Hz), 6.95 (1H, s), 7.03 (1H, d, J = 2.0 Hz), 7.21 (2H, d, J = 8.0 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.54 (1H, dd, J = 8.8, 3.0 Hz), 7.62 (1H, d, J = 3.0 Hz)

Example 234

Methyl 2-[(4-tert-butylbenzyl)oxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 2-(4-tert-butylbenzyl)oxy-5-nitrobenzoate

[0460] ^{1}H-NMR ($CDCl_3$) δ; 1.33 (9H, s), 3.95 (3H, s), 5.28, (2H, s), 7.11 (1H, d, J = 9.2 Hz), 7.42 to 7.46 (4H, m), 8.33 (1H, dd, J = 9.2, 3.0 Hz), 8.73 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-(4-tert-butylbenzyl)oxy benzoate

[0461] ^{1}H-NMR ($CDCl_3$) δ; 1.32 (9H, s), 3.51 (2H, bs), 3.88 (3H, s), 5.05, (2H, s), 6.78 (1H, dd, J = 8.8, 2.8 Hz), 6.88 (1H, d, J = 8.8 Hz), 7.17 (1H, d, J = 2.8 Hz), 7.40 (4H, s)

(3) Methyl 2-[(4-tert-butylbenzyl)oxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0462] A mixed solution of methyl 5-amino-2-(4-tert-butylbenzyl)oxy benzoate (313 mg, 1.0 mmol), 3,4-dimethoxyphenyl isocyanate (0.16 mL, 1.1 mmol) and THF (10 mL) was stirred at room temperature for 16 hours. The solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate and hexane. 365 mg (74%)

^{1}H-NMR ($CDCl_3$) δ; 1.31 (9H, s), 3.88 (3H, s), 3.90 (3H, s) , 3.91 (3H, s), 5.12 (2H, s), 6.82 to 6.89 (4H, m), 6.96 (1H, d, J = 8.8 Hz), 7.08 (1H, s), 7.39 (4H, s), 7.61 (1H, d, J = 2.8 Hz), 7.75 (1H, dd, J = 8.8, 2.8 Hz)

Example 235

Methyl 2-(benzhydryloxy)-5-{[(2,3-dihydro-1-benzofuran-5-ylamino)carbonyl]amino}benzoate

[0463] A mixed solution of methyl 5-amino-2-(benzhydryloxy)benzoate (333 mg, 1.0 mmol), 5-isocyanato-2,3-dihydro-1-benzofuran (161 mg, 1.0 mmol) and THF (10 mL) was stirred at room temperature for 20 hours. The solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate and hexane. 454 mg (92%)

^{1}H-NMR ($CDCl_3$) δ; 3.12 (2H, t, J = 8.6 Hz), 3.86 (3H, s), 4.53 (2H, t, J = 8.6 Hz), 6.20 (1H, s), 6.53 (1H, s), 6.65 (1H, s), 6.69 (1H, d, J = 8.4 Hz), 6.82 (1H, d, J = 8.8 Hz), 6.89 (1H, dd, J = 8.4, 2.2 Hz), 7.14 to 7.51 (12H, m), 7.59 (1H, d, J = 2.8 Hz)

Example 236

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]benzoate

(1) (2-Chlorophenyl)(4-fluorophenyl)methanol

[0464] To a solution (200 mL) of 2-chlorobromobenzene (10.2 g, 53.3 mmol) in THF was added dropwise 1.6N solution of butyl lithium in hexane (40 mL, 65 mmol) at -78°C, the mixture was stirred at -78°C for 10 minutes, a solution (20 mL) of 4-fluorobenzaldehyde (8.0 g, 65.0 mmol) in THF was added dropwise to the mixture, and the mixture was stirred at -78 to -65°C for 1 hour. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 4:1), to obtain the titled compound as oil. 8.1 g (64.2%)

^{1}H-NMR ($CDCl_3$) δ: 2.32 (1H, d, J = 3.8 Hz), 6.22 (1H, d, J = 3.8 Hz), 6.8 to 7.6 (8H, m)

IR (neat) cm^{-1}: 3385, 1723, 1604, 1509, 1225, 1158, 1025, 843, 813, 753, 569

(2) Methyl 2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0465] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.1 g, 10.6 mmol), (2-chlorophenyl)(4-fluorophenyl)methanol (3.00 g, 12.7 mmol), 40% solution of diethyl azodicarbonate in touluen (7.4 g, 17.0 mmol) and a solution (5 mL) of triphenylphosphine (3.3 g, 12.7 mmol) in DMF was stirred at room temperature for 12 hours, the reaction solution was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 20:1), to obtain the titled compound as oil. 1.95 g (44.2%)

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H, s), 6.88 (1H, m), 6.99 (1H, d, J = 9.2 Hz), 7.0 (2H, m), 7.2 to 7.3 (5H, m), 7.4 (1H, m), 7.6 (2H, m)

IR (KBr) cm^{-1}: 1727, 1615, 1586, 1520, 1488, 1438, 1344, 1276, 1246, 1129, 1073, 1000, 820, 748

(3) Methyl 5-amino-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]benzoate

[0466] A mixture of methyl 2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]-5-nitrobenzoate (1.7 g, 4.1 mmol), iron (1.1 g, 20.4 mmol), calcium chloride (222 mg, 2 mmol), ethanol (25 mL) and water (5 mL) was stirred at reflux temperature

for 2 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 3:1), to obtain the titled compound as oil. 1.6 g (100%)

^{1}H-NMR ($CDCl_3$) δ: 3.48 (2H, br), 3.84 (3Hs), 6.59(1H, s), 6.7 (1H, m), 6.9 to 7.4 (7H, m), 7.4 to 7.6 (2H, m), 7.79 (1H, dd, J = 1.7 and 7.8 Hz)

IR (KBr) cm^{-1}: 3452, 1723, 1499, 1445, 1318, 1221, 1078, 755, 732

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]benzoate

[0467] To a solution of methyl 5-amino-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]benzoate (1.4 g, 3.6 mmol) in THF (28 mL) was added 3,4-dimethoxyphenyl isocyanate (0.78 g, 4.4 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 2.1 g (100%)

^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 3.84 (3Hs), 3.86 (3Hs), 6.68 to 6.79 (6H, m), 7.0 (3H, m), 7.15 to 7.24 (2H, m), 7.34 (1H, dd, J = 1.2 and 7.8 Hz), 7.4 (1H, m), 7.5 (2H, m), 7.65 (1H, d, J = 2.7 Hz), 7.73 (1H, dd, J = 1.7 and 7.8 Hz)

IR (KBr) cm^{-1}: 3343, 1731, 1606, 1556, 1511, 1412, 1220, 1159, 1079, 1026, 809, 754

Example 237

N-(tert-butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy] benzamide

(1) 5-({[(3,4-Dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]benzoic acid

[0468] To a solution (30 mL) of methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy]benzoate (1.0 g, 1.77 mmol) in methanol was added 1N aqueous solution of sodium hydroxide (5 mL) at reflux temperature, and the mixture was stirred for 3 hours. The reaction solution was poured into water, and neutralized with 1N-hydrochloric acid. The precipitated crystals were collected by filtration, washed with water, and dried under reduced pressure to obtain the titled compound as a solid. 910 mg (93.3%)

^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 3.87 (3H, s), 6.38 (1H, s), 6.82 (1H, d, J = 8.5 Hz), 6.9(2H, m), 7.1 (3H, m), 7.2 to 7.4 (5H, m), 7.44 (1H, br), 7.59 (1H, br), 7.72 (1H, d, J = 2.7 Hz), 8.26 (1H, dd, J = 2.7 and 9.1 Hz), 11.1 (1H, br)

IR (KBr) cm^{-1}: 3348, 1702, 1606, 1552, 1511, 1418, 1221, 1160, 1025, 812, 755

(2) N-(tert-Butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl)methoxy] benzamide

[0469] A mixed solution of 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4-fluorophenyl) methoxy]benzoic acid (550 mg, 1.0 mmol), 1-hydroxy-1H-benzotriazole (230 mg, 1.5 mmol), tert-butyl amine (146 mg, 2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (240 mg, 1.25 mmol) and DMF (6 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and the precipitates were collected by filtration. This was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 0.93 g (94.4%)

^{1}H-NMR ($CDCl_3$) δ: 1.18 (9H, s), 3.81 (3H, s), 3.83 (3H, s), 6.60 (1H, s), 6.71 to 6.76 (3H, m), 6.92 to 7.81 (14H, m)

IR (KBr) cm^{-1}: 3361, 2964, 1661, 1607, 1511, 1490, 1203, 1028, 755

[0470] According to the same method as Example 236, the compound of Example 238 was synthesized.

Example 238

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{(3-chlorophenyl)(4-fluorophenyl)methoxy}benzoate

(1) Synthesis of (4-fluorophenyl)(3-chlorophenyl)methanol

[0471] ^{1}H-NMR ($CDCl_3$) δ: 2.24 (1H, d, J = 3.4 Hz), 5.80 (1H, d, J = 3.4 Hz), 7.0 (2H, m), 7.2 to 7.4 (6H, m)

IR (neat) cm^{-1}: 3364, 1709, 1604, 1509, 1428, 1225, 1158, 1040, 836, 797, 768, 565

(2) Methyl 2-{(3-chlorophenyl)(4-fluorophenyl)methoxy}-5-nitrobenzoate

[0472] ^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 6.36 (1H, m), 6.98 (1H, d, J = 9.3 Hz), 7.0 (2H, m), 7.26 to 7.39 (3H, m), 7.5

(3H, m), 8.21 (1H, dd, J = 3.0 and 9.3 Hz), 8.74 (1H, d, J = 3.0 Hz)
IR (neat) cm^{-1}: 1727, 1615, 1586, 1520, 1488, 1438, 1344, 1275, 1246, 1129, 1074, 1000, 907, 843, 820, 748

(3) Methyl 5-amino-2-{(3-chlorophenyl)(4-fluorophenyl)methoxy}benzoate

[0473] ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, br), 3.85 (3H, s), 6.06 (1H, m), 6.62 (2H, m), 7.0 (2H, m), 7.13 (1H, dd, J = 1.3 and 2.1 Hz), 7.22 to 7.29 (3H, m), 7.4 (2H, m), 7.5 (1H, m)
IR (neat) cm^{-1}: 1720, 1499, 1221, 1078, 834

(4) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{(3-chlorophenyl)(4-fluorophenyl)methoxy}benzoate

[0474] ^{1}H-NMR($CDCl_3$) δ: 3.85 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.16 (1H, s), 6.48 (1H, s), 6.60 (1H, s), 6.73 (1H, dd, J = 2.3 and 8.5 Hz), 6.8 (3H, m), 7.0 (3H, m), 7.2 to 7.6 (6H, m), 7.61 (1H, d, J = 2.9 Hz)
IR (KBr) cm^{-1}: 3335, 1729, 1606, 1558, 1510, 1413, 1220, 1158, 1079, 1026, 799

[0475] According to the same method as Example 237, the compound of Example 239 was synthesized.

Example 239

N-(tert-Butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(3-chlorophenyl)(4-fluorophenyl)methoxy] benzamide

(1) 5-({[(3,4-Dimethoxyphenyl)amino]carbonyl}amino)-2-{(3-chlorophenyl)(4-fluorophenyl)methoxy}benzoic acid

[0476] ^{1}H-NMR($CDCl_3$) δ: 3.82 (3H, s), 3.85 (3H, s), 6.36 (1H, s), 6.79(1H, d, J = 8.5 Hz), 6.9 (2H, m), 7.1 (2H, m), 7.19 (1H, d, J = 2.4 Hz), 7.25 to 7.37 (6H, m), 7.67 (1H, br), 7.70 (1H, d, J = 2.9 Hz), 7.78 (1H, br), 8.28 (1H, dd, J = 2.9 and 9.1 Hz), 11.2 (1H, br)
IR (KBr) cm^{-1}: 3375, 1693, 1606, 1552, 1511, 1416, 1224, 1161, 1027

(2) N-(tert-Butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(3-chlorophenyl)(4-fluorophenyl)methoxy] benzamide

[0477] ^{1}H-NMR($CDCl_3$) δ: 1.20 (9H, s), 3.81 (3H, s), 3.83 (3H, s), 6.20 (1H, s), 6.7 to 6.8 (3H, m), 7.0 (2H, m), 7.10 (1H, d, J = 1.9 Hz), 7.2 (1H, m), 7.27 to 7.33 (6H, m), 7.59 (1H, br), 7.7 (2H, m), 7.72 (1H, dd, J = 2.8 and 8.9 Hz)
IR (KBr) cm^{-1}: 3358, 2965, 1637, 1607, 1510, 1490, 1203, 1027, 798, 687

[0478] According to the same method as Example 237, the compound of Example 240 was synthesized.

Example 240

N-(tert-Butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl] methoxy}benzamide

(1) 5-({[(3,4-Dimethoxyphenyl)amino]carbonyl}amino)-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoic acid

[0479] ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 3.85 (3H, s), 6.45 (1H, s), 6.80 (1H, d, J = 8.5 Hz), 6.86 to 6.90 (2H, m), 7.0 (2H, m), 7.18 (1H, d, J = 2.2 Hz), 7.3 (2H, m), 7.5 (3H, m), 7.7 (4H, m), 8.26 (1H, dd, J = 2.8 and 9.1 Hz), 11.1 (1H, br)
IR (KBr) cm^{-1}: 3375, 1730, 1606, 1552, 1512, 1416, 1224, 1026

(2) N-(tert-Butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl] methoxy}benzamide

[0480] ^{1}H-NMR($CDCl_3$) δ: 1.18 (9H, s), 3.82 (3H, s), 3.84 (3H, s), 6.28 (1H, s), 6.7 to 6.8 (3H, m), 7.0 (4H, m), 7.2 to 7.3 (2H, m), 7.4 (3H, m), 7.6 (4H, m), 7.74 (1H, dd, J = 2.7 and 9.0 Hz)
IR (KBr) cm^{-1}: 3365, 1660, 1608, 1512, 1490, 1414, 1327, 1205, 1165, 1128, 1067, 1017, 822

Example 241

Methyl 2-[(3,4-dichlorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 5-amino-2-[(3,4-dichlorophenyl)(phenyl)methoxy]benzoate

[0481] To a solution (25 mL) of methyl 2-hydroxy-5-nitrobenzoate (1.08 g, 5.5 mmol), (3,4-dichlorophenyl)(phenyl) methanol (1.40 g, 5.5 mmol) and triphenylphosphine (1.44 g, 5.5 mmol) in acetonitrile was added diethyl azodicarbonate (0.87 mL, 5.5 mmol), and the mixture was stirred at room temperature for 20 hours. The solvent was distilled off under reduced pressure, and the precipitated crystals were filtered off and were washed with toluene. The filtrate was concentrated, the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 5:1). The resulting oil was dissolved in 80% aqueous ethanol solution (30 mL), iron (0.95 g, 17.0 mmol) and calcium chloride (189 mg, 1.7 mmol) were added thereto, and the mixture was heated to reflux for 2 hours. The insolubles were filtered off with Celite in heat, and the filtrate was concentrated, and diluted with water. The mixture was extracted with ethyl acetate, the extracted solution was washed with water and saturated brine, and was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as oil. 0.55 g (2 steps, 25%)

^{1}H-NMR ($CDCl_3$) δ; 3.50 (2H, bs), 3.87 (3H, s), 6.06 (1H, s), 6.63 (2H, d, J = 2.0 Hz), 7.13 to 7.16 (1H, m), 7.28 to 7.46 (7H, m), 7.65 (1H, d, J = 1.8Hz)

(2) Methyl 2-[(3,4-dichlorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0482] A mixed solution of methyl 5-amino-2-[(3,4-dichlorophenyl)(phenyl)methoxy]benzoate (0.55 g, 1.4 mmol), 3,4-dimethoxyphenyl isocyanate (0.21 mL, 1.4 mmol) and THF (10 mL) was stirred at room temperature for 4 hours. The solvent was distilled off under reduced pressure, and the resulting residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as amorphous. 0.58 g (73%)

^{1}H-NMR ($CDCl_3$) δ; 3.82 (3H, s), 3.83 (3H, s), 3.90 (3H, s), 6.12 (1H, s), 6.66 to 6.80 (5H, m), 6.99 (1H, d, J = 2.2 Hz), 7.25 to 7.48 (8H, m), 7.61 (1H, d, J = 2.6 Hz), 7.66 (1H, d, J = 1.8Hz)

Example 242

Methyl 2-[(3,4-difluorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 5-amino-2-[(3,4-difluorophenyl)(phenyl)methoxy]benzoate

[0483] To a solution (30 mL) of 2-hydroxy-5-nitrobenzoate methyl (1.13 g, 5.7 mmol), (3,4-difluorophenyl)(phenyl) methanol (1.26 g, 5.7 mmol) and triphenylphosphine (1.50 g, 5.7 mmol) in acetonitrile was added diethyl azodicarbonate (0.90 mL, 5.7 mmol), and the mixture was stirred at room temperature for 20 hours. The solvent was distilled off under reduced pressure, and the precipitated crystals were filtered off and were washed with toluene. The filtrate was concentrated, and the residue was purified by silicagel column chromatography (hexane:ethyl acetate = 5:1). The resulting oil was dissolved in 80% aqueous ethanol solution (20 mL), iron (0.67 g, 12.0 mmol) and calcium chloride (133 mg, 1.2 mmol) were added thereto, and the mixture was heated to reflux for 2 hours. The insolubles were filtered off with Celite in heat, and the filtrate was concentrated and diluted with water. The mixture was extracted with ethyl acetate, the extracted solution was washed with water and saturated brine, and was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as oil. 0.47 g (2 step, 22%)

^{1}H-NMR ($CDCl_3$) δ; 3.50 (2H, bs), 3.86 (3H, s), 6.07 (1H, s), 6.62 to 6.64 (2H, m), 7.02 to 7.46 (9H, m)

(2) Methyl 2-[(3,4-difluorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0484] A mixed solution of methyl 5-amino-2-[(3,4-difluorophenyl)(phenyl)methoxy]benzoate (455 mg, 1.23 mmol), 3,4-dimethoxyphenyl isocyanate (183 µl, 1.23 mmol) and THF (10 mL) was stirred at room temperature for 16. The solvent was distilled off under reduced pressure, and the resulting residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as amorphous. 32 g (47%)

H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 6.14 (1H, s), 6.65 to 6.81 (5H, m), 6.98 to 7.48 (10H, m), 7.61 (1H, d, J = 2.6 Hz)

[0485] According to the same method as Example 242, the following compounds were obtained.

Example 243

Ethyl 2-{bis[3-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

1) Methyl 2-{bis[3-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0486] H-NMR ($CDCl_3$) δ; 4.02 (3H,s),6.52 (1H,s),6.98 (1H,d,J = 9.6 Hz),7.48 to 7.73 (6H, m), 7.84 (2H, s), 8.24 (1H, dd, J = 9.6, 3.0 Hz), 8.77 (1H, d, J = 3.0 Hz)

(2) Methyl 5-amino-2-{bis[3-(trifluoromethyl)phenyl]methoxy}benzoate

[0487] ^{1}H-NMR ($CDCl_3$) δ; 3.52 (2H, bd), 3.85 (3H,s), 6.22 (1H,s), 6.61 to 6.64 (2H, m), 7.15 to 7.17 (1H, m), 7.42 to 7.66 (6H, m), 7.79 (2H, d, J = 0.8 Hz)

(3) Methyl 2-{bis[3-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0488] ^{1}H-NMR ($CDCl_3$) δ; 3.84 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.31 (1H, s), 6.54 (1H, s), 6.67 to 6.78 (4H, m), 6.98 (1H, d, J = 2.2 Hz), 7.42 to 7.67 (8H, m), 7.81 (2H, s)

Example 244

Ethyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Ethyl 2-[bis(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0489] ^{1}H-NMR ($CDCl_3$) δ; 1.39 (3H, t, J = 7.2 Hz), 4.43 (2H, q, J = 7.2 Hz), 6.40 (1H,s), 6.95 to 7.11 (5H, m), 7.43 to 7.50 (4H, m), 8.20 (1H, dd, J = 9.2, 3.0 Hz), 8.71 (1H, d, J = 3.0 Hz)

(2) Ethyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate

[0490] ^{1}H-NMR ($CDCl_3$) δ; 1.29 (3H, t, J = 7.2 Hz), 3.32 (2H, bd), 4.31 (2H, q, J = 7.2 Hz), 6.11 (1H, s), 6.61 to 6.63 (2H, m), 6.94 to 7.13 (5H, m), 7.36 to 7.47 (4H, m)

(3) Ethyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0491] ^{1}H-NMR ($CDCl_3$) δ; 1.30 (3H, t, J = 7.2 Hz), 3.83 (3H, s), 3.84 (3H, s), 4.33 (2H, q, J = 7.2 Hz), 6.18 (1H, s), 6.66-6.68 (5H, m), 6.95 to 7.05 (5H, m), 7.36 to 7.49 (5H, m), 7.58 (1H, d, J = 2.6 Hz)

Example 245

tert-Butyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl)amino)benzoate

(1) tert-Butyl 2-[bis(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0492] To a solution (10 mL) of tert-butyl 2-hydroxy-5-nitrobenzoate (0.55 g, 2.3 mmol), bis(4-fluorophenyl)methanol (0.51 g, 2.3 mmol) and triphenylphosphine (0.60 g, 2.3 mmol) in acetonitrile was added diethyl azodicarbonate (0.36 mL, 2.3 mmol), and the mixture was stirred at room temperature for 20 hours. The solvent was distilled off under reduced pressure, and the precipitated crystals were filtered off and were washed with toluene. The filtrate was concentrated, and the residue was purified with VARIAN MEGA BOND ELUT NH_2 (60 CC, 20 GRM, hexane:ethyl acetate = 10:1), to obtain the titled compound as oil. 0.61 g (60%)

^{1}H-NMR ($CDCl_3$) δ; 1.55 (9H, s), 6.37 (1H,s), 6.92 (1H, d, J = 9.6 Hz), 7.00 to 7.12 (4H, m), 7.39 to 7.47 (4H, m), 8.15 (1H, dd, J = 9.6, 3.0 Hz), 8.52 (1H, d, J = 3.0 Hz)

(2) tert-Butyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate

[0493] A mixed solution of tert-butyl 2-[bis(4-fluorophenyl)methoxy]-5-nitrobenzoate (353 mg, 0.8 mmol), iron (223 mg, 4.0 mmol), calcium chloride (44 mg, 0.4 mmol) and 80% aqueous ethanol solution (10 mL) was heated to reflux for 3 hours. The insolubles were filtered off with Celite in heat, and the filtrate was concentrated, and diluted with water.

The mixture was extracted with ethyl acetate, and the extracted solution was washed with water and saturated brine and was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified with VARIAN MEGA BOND ELUT SI (60 CC, 10 GRM, hexane:ethyl acetate = 3:1), to obtain the titled compound as oil. 269 mg (82%)

^{1}H-NMR ($CDCl_3$) δ; 1.50 (9H, s), 3.32 (2H, bd), 6.10 (1H, s), 6.55 to 6.57 (2H, m), 6.96 to 7.06 (5H, m), 7.35 to 7.43 (4H, m)

(3) tert-Butyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0494] A mixed solution of tert-butyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (260 mg, 0.63 mmol), 3,4-dimethoxyphenyl isocyanate (0.10 mL, 0.70 mmol) and THF (5 mL) was stirred at room temperature for 16 hours. The solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl acetate and hexane. 246 mg (66%)

^{1}H-NMR ($CDCl_3$) δ; 1.50 (9H, s), 3.84 (3H, s), 3.86 (3H, s), 6. 12 (1H, s), 6.48 (1H, s), 6.56 (1H, s), 6.68 to 6.82 (3H, m), 6.96 to 7.07 (2H, m), 7.34 to 7.42 (6H, m)

Example 246

Isopropyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Isopropyl 2-hydroxy-5-nitrobenzoate

[0495] A mixture of 2-hydroxy-5-nitrobenzoate (10.0 g, 54.0 mmol), 2-propanol (4.13 mL, 54.0 mmol), 1,3-dicyclohexylcarbodiimide (12.2 g, 60.4 mmol) and 4-dimethylaminopyridine (658 mg, 5.40 mmol) in tetrahydrofuran (100 mL) and diethylether (200 mL) was stirred at 0°C for 2 hours and at room temperature for 12 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 9:1), to obtain the titled compound as a solid. 5.70 g (46.7%)

^{1}H-NMR ($CDCl_3$) δ; 1.45 (6H, d, J = 6.4 Hz), 5.30 to 5.42 (1H, m), 7.07 (1H, d, J = 9.2 Hz), 8.33 (1H, dd, J = 9.2, 3.0 Hz), 8.77 (1H, d, J = 3.0 Hz), 11.67 (1H, s)

(2) Isopropyl 2-[bis(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0496] To a solution (20 mL) of iso-propyl 2-hydroxy-5-nitrobenzoate (1.13 g, 5.0 mmol), bis(4-fluorophenyl)methanol (1.10 g, 5.0 mmol) and triphenylphosphine (1.31 g, 5.0 mmol) in acetonitrile was added diethyl azodicarbonate (0.79 mL, 5.0 mmol), and the mixture was stirred at room temperature for 16 hours. The solvent was distilled off under reduced pressure, and the precipitated crystals were filtered off and were washed with toluene. The filtrate was concentrated, and the residue was purified with basic silicagel column chromatography (hexane:ethyl acetate = 5:1), to obtain the titled compound as oil. 983 mg (46%)

^{1}H-NMR ($CDCl_3$) δ; 1.35 (6H, d, J = 6.2 Hz), 5.24 to 5.37 (1H, m), 6.39 (1H, s), 6.66 (1H, d, J = 9.2 Hz), 7.00 to 7.12 (4H, m), 7.42 to 7.49 (4H, m), 8.19 (1H, dd, J = 9.2, 2.8 Hz), 8.65 (1H, d, J = 2.8 Hz)

(3) Isopropyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate

[0497] A mixed solution of isopropyl 2-[bis(4-fluorophenyl)methoxy]-5-nitrobenzoate (975 mg, 2.3 mmol), iron (642 mg, 11.5 mmol), calcium chloride (133 mg, 1.2 mmol) and 80% aqueous ethanol solution (20 mL) was heated to reflux for 2.5 hours. The insolubles were filtered off with Celite in heat, and the filtrate was concentrated, and diluted with water. The mixture was extracted with ethyl acetate, the extracted solution was washed with water and saturated brine, was dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:1), to obtain the titled compound as oil. 799 mg (88%)

^{1}H-NMR ($CDCl_3$) δ; 1.24 (6H, d, J = 6.2 Hz), 3.44 (2H, bd), 5.12 to 5.25 (1H, m), 6.09 (1H, s), 6.56 to 6.58 (2H, m), 6.91 to 7.06 (5H, m), 7.32 to 7.43 (4H, m)

(4) Isopropyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0498] A mixed solution of isopropyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (793 mg, 2.0 mmol), 3,4-dimethoxyphenyl isocyanate (0.39 mL, 2.2 mmol) and THF (10 mL) was stirred at room temperature for 16 hours. The solvent was distilled off under reduced pressure, and the obtained crude crystals were recrystallized from ethyl

acetate and hexane. 1.05 g (91%)

^{1}H-NMR ($CDCl_3$) δ; 1.28 (6H, d, J = 6.2 Hz), 3.84 (3H, s), 3.85 (3H, s), 5.16 to 5.30 (1H, m), 6.20 (1H, s), 6.56 (1H, s), 6.65 (1H, s), 6.67 to 6.82 (3H, m), 6.96 to 7.05 (5H, m), 7.37 to 7.44 (5H, m), 7.53 (1H, d, J = 3.0 Hz)

[0499] The compounds of Example 247 to 279 were synthesized as described below.

[0500] A solution (1.0 mL) of methyl 5-[(anilinocarbonyl)amino]-2-hydroxybenzoate (0.060 mmol), halogenated alkyl (0.070 mmol) and potassium carbonate (0.090 mmol) in DMF was stirred at 60°C for 3 hours. Ethyl acetate (2 mL), water (2.0 mL) and saturated brine (2 mL) were added thereto with shaking. The ethyl acetate layer was taken from a syringe, and was concentrated with Dry Thermo-unit PTU-1C. The residue was purified with preparative HPLC made by Gilson Inc. (PLRP-S column 5 μm 100 A, 50 x 25 mm, 40% to 100% aqueous solution of acetonitrile). The resulting compound was analyzed by LC MASS made by Gilson Inc. (Shiseido capsule pack C18 2 x 5 cm, λ = 220 nm, temperature 40°C, A liquid 0.05% trifluoroacetic acid solution: B liquid acetonitrile: 10 to 95% B liquid (for 4 minutes) 95% B solution (for 1.5 minutes), electrospray ionization mass spectrum).

Example 247

Methyl 5-[(anilinocarbonyl)amino]-2-(propa-2-ynyloxy)benzoate

[0501] 8.1 mg

LC-MS: purity 99%, Rt = 1.82 min, m/z: 325 $[M+H]^+$

Example 248

Methyl 5-[(anilinocarbonyl)amino]-2-[(3-methylbutan-2-enyl)oxy]benzoate

[0502] 7.5 mg

LC-MS: purity 92%, Rt = 2.05 min, m/z: 377 $[M+H]^+$+Na^+

Example 249

Methyl 5-[(anilinocarbonyl)amino]-2-(cyclopentyloxy)benzoate

[0503] 4.4 mg

LC-MS: purity 92%, Rt = 2.07 min, m/z: 355 $[M+H]^+$

Example 250

Methyl 5-[(anilinocarbonyl)amino]-2-{[(2E)-3-phenylpropa-2-enyl]oxy}benzoate

[0504] 8.5 mg

LC-MS: purity 97%, Rt = 2.14 min, m/z: 403 $[M+H]^+$

Example 251

Methyl 5-[(anilinocarbonyl)amino]-2-(2-methoxy-2-oxoethoxy)benzoate

[0505] 7.3 mg

LC-MS: purity 99%, Rt = 1.75 min, m/z: 359 $[M+H]^+$

Example 252

Methyl 5-[(anilinocarbonyl)amino]-2-[(2,5-dimethylbenzyl)oxy]benzoate

[0506] 8.4 mg

LC-MS: purity 99%, Rt = 2.19 min, m/z: 405 $[M+H]^+$

Example 253

Methyl 5-[(anilinocarbonyl)amino]-2-[(4-ethylbenzyl)oxy]benzoate

[0507] 7.3 mg
LC-MS: purity 99%, Rt = 2.21 min, m/z: 405 $[M+H]^+$

Example 254

Methyl 5-[(anilinocarbonyl)amino]-2-[(3,4-dimethylbenzyl)oxy]benzoate

[0508] 8.4 mg
LC-MS: purity 97%, Rt = 2.19 min, m/z: 405 $[M+H]^+$

Example 255

Methyl 5-[(anilinocarbonyl)amino]-2-[(2,4-dimethylbenzyl)oxy]benzoate

[0509] 8.6 mg
LC-MS: purity 99%, Rt = 2.19 min, m/z: 405 $[M+H]^+$

Example 256

Methyl 5-[(anilinocarbonyl)amino]-2-[(4-chlorobenzyl)oxy]benzoate

[0510] 8.5 mg
LC-MS: purity 99%, Rt = 2.16 min, m/z: 411 $[M+H]^+$

Example 257

Methyl 5-[(anilinocarbonyl)amino]-2-[(2,6-difluorobenzyl)oxy]benzoate

[0511] 2.4 mg
LC-MS: purity 99%, Rt = 2.05 min, m/z: 413 $[M+H]^+$

Example 258

Methyl 5-[(anilinocarbonyl)amino]-2-(pyridin-3-ylmethoxy)benzoate

[0512] 8.2 mg
LC-MS: purity 98%, Rt = 1.46 min, m/z: 378 $[M+H]^+$

Example 259

Methyl 5-[(anilinocarbonyl)amino]-2-(pyridin-4-ylmethoxy)benzoate

[0513] 5.4 mg
LC-MS: purity 99%, Rt = 1.45 min, m/z: 378 $[M+H]^+$

Example 260

Methyl 2-[2-(acetyloxy)ethoxy]-5-[(anilinocarbonyl)amino]benzoate

[0514] 6.4 mg
LC-MS: purity 98%, Rt = 1.79 min, m/z: 373 $[M+H]^+$

Example 261

Methyl 5-[(anilinocarbonyl)amino]-2-(1-phenylethoxy)benzoate

[0515] 10.2 mg
LC-MS: purity 98%, Rt = 2.10 min, m/z: 413 $[M+H]^+ + Na^+$

Example 262

Methyl 5-[(anilinocarbonyl)amino]-2-[(4-methylbenzyl)oxy]benzoate

[0516] 6.2 mg,
LC-MS: purity 97%, Rt = 2.13 min, m/z: 391 $[M+H]^+$

Example 263

Methyl 5-[(anilinocarbonyl)amino]-2-(2-phenylethoxy)benzoate

[0517] 4.3 mg
LC-MS: purity 92%, Rt = 2.10 min, m/z: 391 $[M+H]^+$

Example 264

Methyl 5-[(anilinocarbonyl)amino]-2-[(3-methylbenzyl)oxy]benzoate

[0518] 8.8 mg
LC-MS: purity 99%, Rt = 2.13 min, m/z: 391 $[M+H]^+$

Example 265

Methyl 5-[(anilinocarbonyl)amino]-2-[(2-methylbenzyl)oxy]benzoate

[0519] 11.0 mg
LC-MS: purity 99%, Rt = 2.12 min, m/z: 391 $[M+H]^+$

Example 266

Methyl 5-[(anilinocarbonyl)amino]-2-[(2-fluorobenzyl)oxy]benzoate

[0520] 10.5 mg
LC-MS: purity 99%, Rt = 2.08 min, m/z: 395 $[M+H]^+$

Example 267

Methyl 5-[(anilinocarbonyl)amino]-2-[(3-fluorobenzyl)oxy]benzoate

[0521] 10.5 mg
LC-MS: purity 99%, Rt = 2.08 min, m/z: 395 $[M+H]^+$

Example 268

Methyl 5-[(anilinocarbonyl)amino]-2-[(4-fluorobenzyl)oxy]benzoate

[0522] 10.0 mg
LC-MS: purity 96%, Rt = 2.08 min, m/z: 395 $[M+H]^+$

Example 269

Methyl 5-[(anilinocarbonyl)amino]-2-[(3,4-dichlorobenzyl)oxy]benzoate

[0523] 9.9 mg
LC-MS: purity 90%, Rt = 2.25 min, m/z: 445 $[M+H]^+$

Example 270

Methyl 5-[(anilinocarbonyl)amino]-2-[(2-cyanobenzyl)oxy]benzoate

[0524] 1.0 mg
LC-MS: purity 96%, Rt = 1.99 min, m/z: 402 $[M+H]^+$

Example 271

Methyl 5-[(anilinocarbonyl)amino]-2-[(3-cyanobenzyl)oxy]benzoate

[0525] 11.8 mg
LC-MS: purity 96%, Rt = 2.00 min, m/z: 402 $[M+H]^+$

Example 272

Methyl 5-[(anilinocarbonyl)amino]-2-[(4-cyanobenzyl)oxy)benzoate

[0526] 10.3 mg
LC-MS: purity 99%, Rt = 2.00 min, m/z: 402 $[M+H]^+$

Example 273

Methyl 5-[(anilinocarbonyl)amino]-2-(3-phenylpropoxy)benzoate

[0527] 9.5 mg
LC-MS: purity 98%, Rt = 2.18 min, m/z: 405 $[M+H]^+$

Example 274

Methyl 5-[(anilinocarbonyl)amino]-2-[(3-chlorobenzyl)oxy]benzoate

[0528] 11.3 mg
LC-MS: purity 98%, Rt = 2.16 min, m/z: 411 $[M+H]^+$

Example 275

Methyl 5-[(anilinocarbonyl)amino]-2-[(2-chlorobenzyl)oxy]benzoate

[0529] 8.3 mg
LC-MS: purity 97%, Rt = 2.15 min, m/z: 411 $[M+H]^+$

Example 276

Methyl 5-[(anilinocarbonyl)amino]-2-[(2,4-difluorobenzyl)oxy]benzoate

[0530] 6.1 mg
LC-MS: purity 96%, Rt = 2.10 min, m/z: 413 $[M+H]^+$

Example 277

Methyl 5-[(anilinocarbonyl)amino]-2-[(4-nitrobenzyl)oxy]benzoate

[0531] 7.9 mg
LC-MS: purity 98%, Rt = 2.07 min, m/z: 422 $[M+H]^+$

Example 278

Methyl 5-[(anilinocarbonyl)amino]-2-{[4-(methoxycarbonyl)benzyl]oxy}benzoate

[0532] 8.7 mg
LC-MS: purity 99%, Rt = 2.04 min, m/z: 435 $[M+H]^+$

Example 279

Methyl 5-[(anilinocarbonyl)amino]-2-{[3-(trifluoromethyl)benzyl]oxy}benzoate

[0533] 11.8 mg
LC-MS: purity 95%, Rt = 2.19 min, m/z: 445 $[M+H]^+$

Example 280

Methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

(1) (2-Chlorophenyl)[4-(trifluoromethyl)phenyl]methanol

[0534] To a solution THF (200 mL) of 2-chlorobromobenzene (10.2 g, 53.3 mmol) in was added dropwise 1.6N solution of butyl lithium in hexane (40 mL, 65 mmol) at -78°C, the mixture was stirred at -78°C for 10 minutes, a solution of 4-trifluoromethyl benzaldehyde (11.3 g, 65.0 mmol) in THF (20 mL) was added dropwise thereto, and the mixture was stirred at -78 to -65°C for 1 hour. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 4:1), to obtain the titled compound as oil. 6.5 g (42.7%)
^{1}H-NMR ($CDCl_3$) δ: 2.42 (1H, d, J = 3.9 Hz), 6.31 (1H, d, J = 3.9 Hz), 7.2 to 7.4 (3H, m), 7.5 to 7.6 (5H, m)
IR (neat) cm^{-1}: 3385, 1723, 1604, 1509, 1225, 1158, 1025, 843, 813, 753, 569

(2) Methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0535] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.1 g, 10.6 mmol), (2-chlorophenyl)[4-(trifluoromethyl)phenyl] methanol (3.60 g, 12.7 mmol), 40% solution of diethyl azodicarbonate in toluene (7.4 g, 17.0 mmol) and a solution (10 mL) of triphenylphosphine (3.3 g, 12.7 mmol) in acetonitrile was stirred at room temperature for 12 hours, the reaction solution was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 5:1), to obtain the titled compound as oil. 2.4 g (48.6%)
^{1}H-NMR ($CDCl_3$) δ: 3.99 (3H, s), 6.88 (1H, m), 6.96 (1H, s), 6.99 (1H, d, J = 9.4 Hz), 7.2 to 7.3 (2H, m), 7.4 (1H, m), 7.6 (2H, m), 7.80 (2H, d, J = 8.3 Hz), 8.25 (1H, dd, J = 2.9 and 9.4 Hz), 8.75 (1H, d, J = 2.9 Hz)
IR (KBr) cm^{-1}: 1735, 1616, 1524, 1487, 1439, 1347, 1325, 1276, 1127, 1068, 1018, 752

(3) Methyl 5-amino-2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0536] A mixture of methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl)methoxy}-5-nitrobenzoate (2.3 g, 4.9 mmol), iron (1.4 g, 24.7 mmol), calcium chloride (274 mg, 2.5 mmol), ethanol (30 mL) and water (6 mL) was stirred at reflux temperature for 2 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was dried under reduced pressure to obtain the titled compound as oil. 1.9 g (88.2%)
^{1}H-NMR ($CDCl_3$) δ: 3.49 (2H, br), 3.86 (3Hs), 6.69 (3H, m), 7.0 to 7.6 (5H, m), 7.66 (2H, d, J = 7.8 Hz), 7.7 (3H, m)

IR (KBr) cm^{-1}: 3370, 1720, 1499, 1325, 1221, 1126, 1068, 1018, 753

(4) Methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0537] To a solution (20 mL) of methyl 5-amino-2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate (1.7 g, 3.6 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.84 g, 4.7 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 1.6 g (66.8%)

^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 3.85 (3Hs), 3.88 (3Hs), 6.52 (1H, brs), 6.63 (1H, brs), 6.72 (1H, dd, J = 2.4 Hz), 6.78 (1H, d, J = 4.4 Hz), 6.81 (2H, 8.5 Hz), 6.99 (1H, d, J = 2.4 Hz), 7.18 to 7.25 (2H, m), 7.36 (1H, dd, J = 1.5 Hz), 7.47 (1H, dd, J = 2.8 and 8.9 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.66 (1H, d, J = 2.8 Hz), 7.70 (1H, dd, J = 2.0 and 7.6 Hz), 7.75 (2H, d, J = 8.4 Hz)

IR (KBr) cm^{-1}: 3346, 1732, 1610, 1550, 1498, 1414, 1326, 1221, 1165, 1125, 1068, 1017, 810, 755

Example 281

N-(tert-Butyl)-2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

(1) 2-{(2-Chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0538] To a solution (30 mL) of methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate (0.9 g, 1.46 mmol) in methanol was added 1N aqueous solution of sodium hydroxide (5 mL) at reflux temperature, and the mixture was stirred for 3 hours. The reaction solution was poured into water, and neutralized with 1N-hydrochloric acid. The precipitated crystals were collected, washed with water, and dried under reduced pressure to obtain the titled compound as a solid. 800 mg (91.0%)

^{1}H-NMR ($CDCl_3$) δ: 3.81 (3H, s), 3.84 (3H, s), 6.74 to 6.89 (4H, m), 7.19 to 7.76 (13H, m), 8.23 (1H, dd, J = 2.8 and 9.2 Hz), 11.0 (1H, br)

IR (KBr) cm^{-1}: 3336, 1697, 1609, 1556, 1514, 1419, 1325, 1221, 1166, 1129, 1068, 1018, 910, 812, 755, 733

(2) N-(tert-Butyl)-2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

[0539] A mixed solution of 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino] carbonyl}amino)benzoate (300 mg, 0.5 mmol), 1-hydroxy-1H-benzotriazole (115 mg, 0.75 mmol), tert-butyl amine (105 mg, 1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (120 mg, 0.63 mmol) and DMF (3 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and the precipitates were collected. This was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 0.24 g (74.7%)

1H-NMR ($CDCl_3$) δ: 1.17 (9H, s), 3.84 (3H, s), 3.85 (3H, s), 6.6 to 6.8 (4H, m), 6.99 (1H, brs), 7.08 (1H, d, J = 3.0 Hz,), 7.3 (4H, m), 7.4 (1H, m), 7.50 (2H, d, J = 8.0 Hz), 7.57 (1H, s), 7.6 (3H, m), 7.74 (1H, dd, J = 2.8 and 8.9 Hz)

IR (KBr) cm^{-1}: 3361, 2954, 1727, 1652, 1609, 1556, 1514, 1498, 1466, 1439, 14.15, 1326, 1222, 1165, 1127, 1068, 1018, 909, 810, 733

[0540] According to the same method as Example 280, the compound of Example 282 was synthesized.

Example 282

Methyl 2-{(2-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

(1) (2-Fluorophenyl)[4-(trifluoromethyl)phenyl]methanol

[0541] ^{1}H-NMR ($CDCl_3$) δ: 2.37 (1H, d, J = 3.8 Hz), 6.31 (1H, d, J = 4.1 Hz), 7.0 to 7.1 (1H, m), 7.16 (1H, td, 1.2 and 7.4 Hz), 7.27 to 7.31 (1H, m), 7.46 (1H, td, J = 1.7 and 7.4 Hz), 7.54 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz)

IR (neat) cm^{-1}: 3375, 1710, 1620, 1588, 1488, 1458, 1418, 1326, 1230, 1165, 1126, 1068, 1017, 820, 759

(2) Methyl 2-{(2-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0542] ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 6.85 (1H, s), 7.03 (1H, d, J = 9.3 Hz), 7.13 (1H, ddd, J = 1.22, 8.3, and 10.3 Hz), 7.2 to 7.3 (1H, m), 7.6 (3H, m), 7.75 (2H, d, J = 8.1 Hz), 8.24 (1H, dd, J = 2.9 and 9.3 Hz), 8.76 (1H, d, J = 2.9 Hz)
IR (KBr) cm^{-1}: 1736, 1615, 1586, 1524, 1488, 1348, 1326, 1277, 1128, 1068, 1017, 826, 760

(3) Methyl 5-amino-2-{(2-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0543] ^{1}H-NMR ($CDCl_3$) δ: 3.55 (2H, br), 3.86 (3H, s), 6.57 (1H, m), 6.7 (2H, m), 7.0 to 7.5 (4H, m), 7.58 (2H, d, J = 7.8 Hz), 7.7 (3H, m)
IR (KBr) cm^{-1}: 3375, 1723, 1621, 1499, 1326, 1222, 1166, 1125, 1068, 1018, 760

(4) Methyl 2-{(2-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0544] ^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 6.47 (1H, s), 6.59 (1H, s), 6.66 (1H, s), 6.73 (1H, dd, J = 2.4 and 8.5 Hz), 6.80 (1H, d, J = 8.5 Hz), 6.85 (1H, d, J = 9.0 Hz), 6.98 (1H, d, J = 2.4 Hz), 7.0 (1H, m), 7.1 (1H, m), 7.2 (1H, m), 7.47 (1H, dd, J = 2.8 and 9.0 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.71 (2H, d, J = 8.4 Hz)
IR (KBr) cm^{-1}: 3345, 1727, 1606, 1554, 1477, 1326, 1221, 1165, 1124, 1068, 1018, 762

[0545] According to the same method as Example 281, the compound of Example 283 was synthesized.

Example 283

N-(tert-Butyl)-2-{(2-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

(1) 2-{(2-Fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0546] ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 3.85 (3H, s), 6.78 (1H, m), 6.81 (1H, s), 6.90 (1H, dd, 2.4 and 8.5 Hz), 6.93 (1H, d, J = 9.3 Hz), 7.14 to 7.21 (3H, m), 7.3 to 7.4 (2H, m), 7.57 (2H, d, J = 8.1 Hz), 7.57 (1H, brs), 7.67 (2H, d, J = 8.1 Hz), 7.70 (1H, brs), 7.73 (1H, d, J = 2.6 Hz), 8.25 (1H, dd, J = 2.6 and 9.3), 11.0 (1H, br)
IR (KBr) cm^{-1}: 3294, 1676, 1540, 1497, 1454, 1327, 1300, 1259, 1221, 1167, 1135, 1067, 1020, 815, 764

(2) N-(tert-Butyl)-2-{(2-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

[0547] ^{1}H-NMR (CDC13) δ: 1.22 (9H, s), 3.81 (3H, s), 3.83 (3H, s), 6.59 (1H, s), 6.7 (3H, m), 7.1 (3H, m), 7.3 (4H, m), 7.51 (2H, d, J = 8.3 Hz), 7.56 (1H, s), 7.6 (3H, m), 7.71 (1H, dd, J = 2.8 and 8.9 Hz)
IR (KBr) cm^{-1}: 3347, 2968, 1637, 1610, 1543, 1515, 1491, 1456, 1326, 1207, 1167, 1130, 1068, 1028, 911, 760, 734

[0548] According to the same method as Example 280, the compound of Example 284 was synthesized.

Example 284

Methyl 2-{(3-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

(1) (3-Chlorophenyl)[4-(trifluoromethyl)phenyl]methanol

[0549] ^{1}H-NMR ($CDCl_3$) δ: 2.37 (1H, d, J = 2.9 Hz), 5.86 (1H, brs), 7.22 to 7.31 (3H, m), 7.38 (1H, s), 7.50 (2H, d, J = 8.2 Hz), 7.61 (2H, d, J = 8.2 Hz)
IR (neat) cm^{-1}. 3406, 1710, 1620, 1597, 1476, 1417, 1376, 1327, 1260, 1166, 1126, 1068, 1045, 1017, 846, 787, 762

(2) Methyl 2-{(3-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0550] ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 6.85 (1H, s), 7.03 (1H, d, J = 9.3 Hz), 7.13 (1H, ddd, J = 1.22, 8.3, and 10.3

Hz), 7.2 to 7.3 (2H, m), 7.6 (3H, m), 7.75 (2H, d, J = 8.1 Hz), 8.24 (1H, dd, J = 2.9 and 9.3 Hz), 8.76 (1H, d, J = 2.9 Hz)
IR (KBr) cm^{-1}: 1736, 1615, 1589, 1524, 1486, 1347, 1326, 1277, 1128, 1068, 1017, 825, 748

(3) Methyl 5-amino-2-{(3-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0551] ^{1}H-NMR ($CDCl_3$) δ: 3.51 (2H, br), 3.86 (3H, s), 6.12 (1H, s), 6.6 (2H, m), 7.15 (1H, d, J = 2.4 Hz), 7.22 to 7.34 (3H, m), 7.50 (1H, s), 7.6 (4H, m)
IR (KBr) cm^{-1}: 1722, 1499, 1325, 1222, 1124, 1067, 1018, 787

(4) Methyl 2-{(3-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0552] ^{1}H-NMR ($CDCl_3$) δ: 3.81 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 6.17 (1H, s), 6.63 (1H, s), 6.6 to 6.8 (3H, m), 6.81 (1H, brs), 6.91 (1H, brs), 6.99(1H, d, J = 2.2 Hz), 7.22 to 7.33 (2H, m), 7.45 (1H, dd, J = 3.9 and 9.0 Hz), 7.51 (1H, brs), 7.60 (5H, m)
IR (KBr) cm^{-1}: 3334, 1725, 1654, 1608, 1556, 1523, 1498, 1326, 1220, 1165, 1127, 1067, 1018, 767

[0553] According to the same method as Example 281, the compound of Example 285 was synthesized.

Example 285

N-(tert-Butyl)-2-{(3-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

(1) 2-{(3-Chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0554] ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 3.85 (3H, s), 6.40 (1H, s), 6.80 (1H, d, J = 8.8 Hz), 6.9(2H, m), 7.15 (1H, d, J = 2.4 Hz), 7.2 to 7.4 (4H, m), 7.5 (3H, m), 7.64 (1H, brs), 7.67 (2H, d, J = 8.3 Hz), 7.71 (1H, d, J = 2.8 Hz) 8.22 (1H, dd, J = 2.8 and 9.2 Hz), 11.0 (1H, br)
IR (KBr) cm^{-1}: 3308, 1703, 1555, 1495, 1325, 1222, 1128, 1068, 1018

(2) N-(tert-Butyl)-2-{(3-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

[0555] ^{1}H-NMR ($CDCl_3$) δ: 1.21 (9H, s), 3.81 (3H, s), 3.82 (3H, s), 6.24 (1H, s), 6.68 to 6.76 (3H, m), 7.10 (1H, s) 7.2 (1H, m), 7.30 to 7.34 (4H, m), 7.45 (2H, d, J = 8.1 Hz), 7.6 (5H, m), 7.71 (1H, dd, J = 2.6 and 8.9 Hz)
IR (KBr) cm^{-1}: 3370, 1640, 1514, 1493, 1326, 1206, 1167, 1130, 1068, 1018, 734

[0556] According to the same method as Example 280, the compound of Example 286 was synthesized.

Example 286

Methyl 2-{(3-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

(1) (3-Fluorophenyl)[4-(trifluoromethyl)phenyl]methanol

[0557] ^{1}H-NMR ($CDCl_3$) δ: 2.38 (1H, d, J = 3.1 Hz), 5.87 (1H, d, J = 3.1 Hz), 7.0 (1H, m), 7.07 to 7.14 (2H, m), 7.28 to 7.34 (1H, m), 7.50 (2H, d, J = 8.2 Hz), 7.60 (2H, d, 8.3 Hz)
IR (neat) cm^{-1}: 3405, 1710, 1614, 1592, 1487, 1450, 1415, 1377, 1327, 1251, 1167, 1127, 1068, 1017, 851, 762

(2) Methyl 2-{(3-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-nitrobenzoate

[0558] ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 6.44 (1H, s), 7.0 (2H, m), 7.2 to 7.3 (3H, m), 7.64 (2H, d, J = 8.4 Hz), 7.68 (2H, d, J = 8.4 Hz), 8.22 (1H, dd, J = 2.8 and 8.1 Hz), 8.76 (1H, d, J = 2.8 Hz)
IR (KBr) cm^{-1}: 1734, 1615, 1591, 1523, 1488, 1348, 1326, 1277, 1167, 1128, 1068, 1016, 823, 777, 748

(3) Methyl 5-amino-2-{(3-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}benzoate

[0559] ^{1}H-NMR ($CDCl_3$) δ: 3.51 (2H, brs), 3.85 (3H, s), 6.15 (1H, m), 6.6 (2H, m), 7.0 (1H, m), 7.1 (1H, m), 7.2 to 7.3 (3H, m), 7.59 (2H, d, J = 8.7 Hz), 7.62 (2H, d, J = 8.7 Hz)
IR (KBr) cm^{-1}: 3374, 1721, 1615, 1592, 1500, 1326, 1222, 1125, 1067, 1018, 789

(4) Methyl 2-{(3-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0560] ^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 6.21 (1H, s), 6.68 to 6.81 (5H, m), 6.92 to 6.97 (1H, m), 6.99 (1H, d, J = 2.2 Hz), 7.20 to 7.30 (3H, m), 7.46 (1H, dd, J = 2.9 and 9.0 Hz), 7.6 (5H, m)
IR (KBr) cm^{-1}: 3344, 1710, 1654, 1613, 1558, 1497, 1416, 1326, 1222, 1166, 1129, 1068, 1018, 731

[0561] According to the same method as Example 281, the compound of Example 287 was synthesized.

Example 287

N-(tert-Butyl)-2-{(3-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

(1) 2-{(3-Fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzoate

[0562] ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 3.86 (3H, s), 6.43 (1H, s), 6.80 (1H, d, J = 8.7 Hz), 6.9(2H, m), 7.0 to 7.2 (4H, m), 7.3 to 7.5 (2H, m), 7.52 (2H, d, J = 8.3 Hz), 7.61 (1H, brs), 7.68 (2H, d, J = 8.3 Hz), 7.71 (1H, d, J = 3.0 Hz), 8.23 (1H, dd, J = 2.6 and 9.2 Hz), 11.0 (1H, br)
R (KBr) cm^{-1}: 3308, 1704, 1613, 1556, 1515, 1495, 1325, 1225, 1130, 1068, 1018, 763

(2) N-(tert-Butyl)-2-{(3-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzamide

[0563] ^{1}H-NMR($CDCl_3$) δ: 1.20 (9H, s), 3.82 (3H, s), 3.84 (3H, s), 6.27 (1H, s), 6.7 to 6.8 (3H, m), 7.0 to 7.2 (5H, m), 7.19 (1H, s), 7.3 (1H, m), 7.46 (2H, d, J = 7.8 Hz), 7.56 (1H, s), 7.6 (3H, m), 7.71 (1H, dd, J = 2.8 and 8.9 Hz)
IR (KBr) cm^{-1}: 3346, 1636, 1515, 1490, 1326, 1206, 1167, 1131, 1068

Example 288

5-({[(3,4-Dimethoxyphenyl)amino]carbonyl}amino)-2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-N-isopropyl benzamide

[0564] A mixture of 2-{(4-fluorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate (200 mg, 0.34 mmol), 1-hydroxy-1H-benzotriazole (78 mg, 0.51 mmol), iso-propyl amine (0.58 mL, 0.68 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (82 mg, 0.43 mmol) and DMF (2 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, and was poured into water, and the precipitates were collected. This was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 210 mg (98.7%)
^{1}H-NMR(400 MHz) δ: 0.94 (6H, s), 3.82 (6H, s), 4.10 (1H, t, J = 6.6 Hz), 6.31 (1H, s), 6.68 to 6.77 (3H, m), 7.0 (2H, s) 7.12 (1H, s), 7.2 (2H, m), 7.46 (2H, d, J = 7.8 Hz), 7.64 (2H, d, J = 7.8 Hz), 7.77 (1H, s), 7.9 to 8.11 (3H, m), 8.23 (1H, s)
IR (KBr) cm^{-1}: 3348, 1635, 1607, 1511, 1491, 1326, 1205, 1166, 1129, 1068, 1017, 824, 734

[0565] The compounds of Example 289 to 377 were synthesized as described below.

[0566] To a solution (1 mL) of methyl 5-amino-2-benzhydryloxy benzoate (0.900 mmol) and diisopropylethyl amine (0.108 mmol) in acetonitrile was added N,N-disuccinimidyl carbamate (0.108 mmol) at 0°C, and the mixture was stirred at 0°C for 40 minutes. This solution was added to a solution of diisopropylethyl amine (0.108 mmol) and amine (0.09 mmol), and the mixture was stirred for 12 hours at room temperature. The solvent was evaporated with Dry Thermo-unit, to the residue were added water and dichloromethane, the layer of dichloromethane was separated with PTFE filter (1 μm pore size, Whatman Inc.). Dichloromethane was evaporated with Dry Thermo-unit, and the residue was purified with preparative HPLC (PLRP-S column 5 μm 100 A, 50 x 25 mm, 40% to 100% aqueous solution of acetonitrile). The resulting cbmpound was analyzed by LC MASS made by Gilson Inc. (Shiseido capsule pack C18 2 x 5

cm, λ = 220 nm, temperature 40°C, A liquid 0.05% trifluoroacetic acid solution: B liquid acetonitrile: 10 to 95% B liquid (for 4 minutes) 95% B liquid (for 1.5 minutes), electrospray ionization mass spectrum).

Example 289

Methyl 2-(benzhydryloxy)-5-{[(butylamino)carbonyl]amino}benzoate

[0567] 20.0 mg, LC-MS: purity 95%, Rt = 3.56 mjn, m/z: 433 $[M+H]^+$

Example 290

Methyl 2-(benzhydryloxy)-5-({[(cyclohexylmethyl)amino]carbonyl}amino)benzoate

[0568] 22.3 mg, LC-MS: purity 95%, Rt = 3.86 mjn, m/z: 473 $[M+H]^+$

Example 291

Methyl 2-(benzhydryloxy)-5-{[(cyclopropylamino)carbonyl]amino}benzoate

[0569] 21.2 mg, LC-MS: purity 92%, Rt = 3.25 mjn, m/z: 417 $[M+H]^+$

Example 292

Methyl 2-(benzhydryloxy)-5-{[(benzylamino)carbonyl]amino}benzoate

[0570] 21.5 mg, LC-MS: purity 99%, Rt = 3.58 mjn, m/z: 467 $[M+H]^+$

Example 293

Methyl 2-(benzhydryloxy)-5-({[(1,3-benzodioxol-5-ylmethyl)amino]carbonyl}amino)benzoate

[0571] 27.5 mg, LC-MS: purity 97%, Rt = 3.53 mjn, m/z: 511 $[M+H]^+$

Example 294

Methyl 2-(benzhydryloxy)-5-({[(2-phenylethyl)amino]carbonyl}amino)benzoate

[0572] 21.5 mg, LC-MS: purity 99%, Rt = 3.67 mjn, m/z: 481 $[M+H]^+$

Example 295

Methyl 2-(benzhydryloxy)-5-({[(3-phenylpropyl)amino]carbonyl}amino)benzoate

[0573] 24.5 mg, LC-MS: purity 99%, Rt = 3.77 mjn, m/z: 495 $[M+H]^+$

Example 296

Methyl 5-{[(benzhydrylamino)carbonyl]amino}-2-(benzhydryloxy)benzoate

[0574] 23.3 mg, LC-MS: purity 89%, Rt = 3.93 mjn, m/z: 543 $[M+H]^+$

Example 297

Methyl 2-(benzhydryloxy)-5-({[(2-methoxyethyl)amino]carbonyl}amino)benzoate

[0575] 21.8 mg, LC-MS: purity 97%, Rt = 3.18 mjn, m/z: 435 $[M+H]^+$

Example 298

Methyl 2-(benzhydryloxy)-5-[({[3-(methylthio)propyl]amino}carbonyl)amino]benzoate

[0576] 24.0 mg, LC-MS: purity 98%, Rt = 3.45 mjn, m/z: 465 $[M+H]^+$

Example 299

Methyl 2-(benzhydryloxy)-5-({[(tetrahydrofuran -2-ylmethyl)amino]carbonyl}amino)benzoate

[0577] 21.0 mg, LC-MS: purity 100%, Rt = 3.27 mjn, m/z: 461 $[M+H]^+$

Example 300

Methyl 2-(benzhydryloxy)-5-[({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)amino]benzoate

[0578] 26.3 mg, LC-MS: purity 99%, Rt = 3.59 mjn, m/z: 520 $[M+H]^+$

Example 301

Methyl 2-(benzhydryloxy)-5-({[(1-ethylpropyl)amino]carbonyl}amino)benzoate

[0579] 19.0 mg, LC-MS: purity 99%, Rt = 3.64 mjn, m/z: 447 $[M+H]^+$

Example 302

Methyl 2-(benzhydryloxy)-5-{[(tert-butylamino)carbonyl]amino}benzoate

[0580] 18.0 mg, LC-MS: purity 96%, Rt = 3.63 mjn, m/z: 455 $[M+H]^+$

Example 303

Methyl 2-(benzhydryloxy)-5-{[(cyclohexylamino)carbonyl]amino}benzoate

[0581] 22.4 mg, LC-MS: purity 97%, Rt = 3.71 mjn, m/z: 459 $[M+H]^+$

Example 304

Methyl 2-(benzhydryloxy)-5-{[(propa-2-ynylamino)carbonyl]amino}benzoate

[0582] 17.4 mg, LC-MS: purity 97%, Rt = 3.27 mjn, m/z: 437 $[M+H]^+$

Example 305

Methyl 2-(benzhydryloxy)-5-[({[4-(trifluoromethyl)benzyl]amino}carbonyl)amino]benzoate

[0583] 22.4 mg, LC-MS: purity 99%, Rt = 3.83 mjn, m/z: 535 $[M+H]^+$

Example 306

Methyl 2-(benzhydryloxy)-5-[({[2-(3,4-dimethoxyphenyl)ethyl]amino}carbonyl)amino]benzoate

[0584] 26.5 mg, LC-MS: purity 90%, Rt = 3.49 mjn, m/z: 541 $[M+H]^+$

Example 307

Methyl 2-(benzhydryloxy)-5-({[(3,3-diphenylpropyl)amino]carbonyl}amino)benzoate

[0585] 32.4 mg, LC-MS: purity 92%, Rt = 4.02 mjn, m/z: 571 $[M+H]^+$

Example 308

Methyl 2-(benzhydryloxy)-5-{[(2,3-dihydro-1H-indene-2-ylamino)carbonyl]amino}benzoate

[0586] 23.6 mg, LC-MS: purity 99%, Rt = 3.74 mjn, m/z: 493 $[M+H]^+$

Example 309

Methyl 2-(benzhydryloxy)-5-({[(3-isopropoxypropyl)amino]carbonyl}amino)benzoate

[0587] 22.9 mg, LC-MS: purity 99%, Rt = 3.48 mjn, m/z: 477 $[M+H]^+$

Example 310

Methyl 2-(benzhydryloxy)-5-({[(2-oxoazepan-3-yl)amino]carbonyl}amino)benzoate

[0588] 23.0 mg, LC-MS: purity 97%, Rt = 3.19 mjn, m/z: 488 $[M+H]^+$

Example 311

Methyl 2-(benzhydryloxy)-5-({[(2-furylmethyl)amino]carbonyl}amino)benzoate

[0589] 23.4 mg, LC-MS: purity 97%, Rt = 3.44 mjn, m/z: 457 $[M+H]^+$

Example 312

Methyl 2-(benzhydryloxy)-5-[({[3-(2-oxypyrrolidin-1-yl)propyl)amino}carbonyl)amino]benzoate

[0590] 24.1 mg, LC-MS: purity 96%, Rt = 3.08 mjn, m/z: 502 $[M+H]^+$

Example 313

Methyl 2-(benzhydryloxy)-5-{[(dipropylamino)carbonyl]amino}benzoate

[0591] 19.8 mg, LC-MS: purity 100%, Rt = 3.85 mjn, m/z: 461 $[M+H]^+$

Example 314

Methyl 2-(benzhydryloxy)-5-({[methyl(1-naphthylmethyl)amino]carbonyl}amino)benzoate

[0592] 29.4 mg, LC-MS: purity 92%, Rt = 3.97 mjn, m/z: 531 $[M+H]^+$

Example 315

Methyl 2-(benzhydryloxy)-5-({[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]carbonyl}amino)benzoate

[0593] 24.4 mg, LC-MS: purity 98%, Rt = 3.58 mjn, m/z: 555 $[M+H]^+$

Example 316

Methyl 2-(benzhydryloxy)-5-({[bis(2-methoxyethyl)amino]carbonyl}amino)benzoate

[0594] 22.6 mg, LC-MS: purity 98%, Rt = 3.54 mjn, m/z: 493 $[M+H]^+$

Example 317

Methyl 2-(benzhydryloxy)-5-[(piperidin-1-ylcarbonyl)amino]benzoate

[0595] 21.3 mg, LC-MS: purity 99%, Rt = 3.57 mjn, m/z: 445 $[M+H]^+$

Example 318

Methyl 2-(benzhydryloxy)-5-{[(2,6-dimethylmorpholin-4-yl)carbonyl]amino}benzoate

[0596] 22.5 mg, LC-MS: purity 99%, Rt = 3.47 mjn, m/z: 475 $[M+H]^+$

Example 319

Methyl 2-(benzhydryloxy)-5-[(3,4-dihydroisoquinolin-2 (1H)-ylcarbonyl)amino]benzoate

[0597] 22.5 mg, LC-MS: purity 99%, Rt = 3.76 mjn, m/z: 493 $[M+H]^+$

Example 320

Methyl 5-({[4-(aminocarbonyl)piperidin-1-yl]carbonyl}amino)-2-(benzhydryloxy)benzoate

[0598] 21.3 mg, LC-MS: purity 97%, Rt = 2.95 mjn, m/z: 488 $[M+H]^+$

Example 321

Methyl 2-(benzhydryloxy)-5-({[4-(2-hydroxyethyl)piperidin-1-yl]carbonyl}amino)benzoate

[0599] 24.6 mg, LC-MS: purity 97%, Rt = 3.19 mjn, m/z: 489 $[M+H]^+$

Example 322

Methyl 2-(benzhydryloxy)-5-[(thiomorpholin-4-ylcarbonyl)amino]benzoate

[0600] 24.9 mg, LC-MS: purity 98%, Rt = 3.46 mjn, m/z: 463 $[M+H]^+$

Example 323

Methyl 2-(benzhydryloxy)-5-{[(4-benzylpiperidin-1-yl)carbonyl]amino}benzoate

[0601] 26.7 mg, LC-MS: purity 91%, Rt = 4.07 mjn, m/z: 535 $[M+H]^+$

Example 324

Methyl 5-({[3-(acetylamino)pyrrolidin-1-yl]carbonyl}amino)-2-(benzhydryloxy)benzoate

[0602] 24.7 mg, LC-MS: purity 98%, Rt = 2.95 mjn, m/z: 488 $[M+H]^+$

Example 325

Methyl 2-(benzhydryloxy)-5-({[cyclohexyl(methyl)amino]carbonyl}amino)benzoate

[0603] 21.3 mg, LC-MS: purity 99%, Rt = 3.86 mjn, m/z: 473 $[M+H]^+$

Example 326

Methyl 2-(benzhydryloxy)-5-({[benzyl(methyl)amino]carbonyl}amino)benzoate

[0604] 21.1 mg, LC-MS: purity 98%, Rt = 3.72 mjn, m/z: 481 $[M+H]^+$

Example 327

N-({[4-(benzhydryloxy)-3-(methoxycarbonyl)phenyl]amino}carbonyl)-N-benzyl-beta-alanine ethyl ester

[0605] 22.9 mg, LC-MS: purity 98%, Rt = 3.84 mjn, m/z: 567 $[M+H]^+$

Example 328

Methyl 2-(benzhydryloxy)-5-({[ethyl(2-methoxyethyl)amino]carbonyl}amino)benzoate

[0606] 23.2 mg, LC-MS: purity 96%, Rt = 3.53 mjn, m/z: 463 $[M+H]^+$

Example 329

Methyl 2-(benzhydryloxy)-5-{[(3,5-dimethylpiperidin-1-yl)carbonyl]amino}benzoate

[0607] 20.6 mg, LC-MS: purity 99%, Rt = 3.92 mjn, m/z: 473 $[M+H]^+$

Example 330

Methyl 2-(benzhydryloxy)-5-[(octahydroisoquinolin-2 (1H)-ylcarbonyl)amino]benzoate

[0608] 26.2 mg, LC-MS: purity 99%, Rt = 4.03 mjn, m/z: 499 $[M+H]^+$

Example 331

Ethyl 1-({[4-(benzhydryloxy)-3-(methoxycarbonyl)phenyl]amino}carbonyl)piperidin-4carbonate

[0609] 25.5 mg, LC-MS: purity 99%, Rt = 3.57 mjn, m/z: 517 $[M+H]^+$

Example 332

Methyl 2-(benzhydryloxy)-5-{[(4-hydroxypiperidin-1-yl)carbonyl]amino}benzoate

[0610] 23.8 mg, LC-MS: purity 99%, Rt = 3.03 mjn, m/z: 461 $[M+H]^+$

Example 333

Methyl 2-(benzhydryloxy)-5-{[(3-{[(2,6-dimethylphenyl)amino]methyl}pyrrolidin-1-yl)carbonyl]amino}benzoate

[0611] 31.4 mg, LC-MS: purity 90%, Rt = 3.06 mjn, m/z: 564 $[M+H]^+$

Example 334

Methyl 2-(benzhydryloxy)-5-({[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]carbonyl}amino)benzoate

[0612] 30.6 mg, LC-MS: purity 98%, Rt = 3.69 mjn, m/z: 572 $[M+H]^+$

Example 335

Methyl 5-[({3-[acetyl(ethyl)amino]pyrrolidin-1-yl}carbonyl)amino]-2-(benzhydryloxy)benzoate

[0613] 29.6 mg, LC-MS: purity 98%, Rt = 3.16 mjn, m/z: 516 $[M+H]^+$

Example 336

Methyl 2-(benzhydryloxy)-5-{[(1,3-benzothiazol-2-ylamino)carbonyl]amino}benzoate

[0614] 22.6 mg, LC-MS: purity 92%, Rt = 3.82 mjn, m/z: 510 $[M+H]^+$

Example 337

Methyl 2-(benzhydryloxy)-5-[({[4-(methoxycarbonyl)phenyl]amino}carbonyl)amino]benzoate

[0615] 14.9 mg, LC-MS: purity 99%, Rt = 3.61 mjn, m/z: 533 $[M+H]^+$

Example 338

Methyl 2-(benzhydryloxy)-5-({[(2-chloro-4-cyanophenyl)amino]carbonyl}amino)benzoate

[0616] 1.8 mg, LC-MS: purity 84%, Rt = 3.86 mjn, m/z: 512 $[M+H]^+$

Example 339

Methyl 2-(benzhydryloxy)-5-({[(3-chloro-4-cyanophenyl)amino]carbonyl}amino)benzoate

[0617] 6.5 mg, LC-MS: purity 92%, Rt = 3.85 mjn, m/z: 512 $[M+H]^+$

Example 340

Methyl 2-(benzhydryloxy)-5-({[(3,5-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0618] 18.9 mg, LC-MS: purity 98%, Rt = 3.67 mjn, m/z: 513 $[M+H]^+$

Example 341

Methyl 2-(benzhydryloxy)-5-[({[2-(1H-pyrrol-1-yl)phenyl]amino}carbonyl)amino]benzoate

[0619] 18.0 mg, LC-MS: purity 92%, Rt = 3.93 mjn, m/z: 518 $[M+H]^+$

Example 342

Methyl 2-(benzhydryloxy)-5-[({[3-(trifluoromethyl)phenyl]amino}carbonyl)amino]benzoate

[0620] 21.3 mg, LC-MS: purity 98%, Rt = 3.97 mjn, m/z: 543 $[M+Na]^+$

Example 343

Methyl 2-(benzhydryloxy)-5-({[(3,4-dichlorophenyl)amino]carbonyl}amino)benzoate

[0621] 21.2 mg, LC-MS: purity 95%, Rt = 4.09 mjn, m/z: 543 $[M+Na]^+$

Example 344

Methyl 2-(benzhydryloxy)-5-({[(4-pentylphenyl)amino]carbonyl}amino)benzoate

[0622] 27.2 mg, LC-MS: purity 100%, Rt = 4.35 mjn, m/z: 523 $[M+H]^+$

Example 345

Methyl 2-(benzhydryloxy)-5-({[(4-cyano-1-naphthyl)amino]carbonyl}amino)benzoate

[0623] 6.0 mg, LC-MS: purity 94%, Rt = 3.88 mjn, m/z: 550 $[M+Na]^+$

Example 346

Methyl 2-(benzhydryloxy)-5-{[(1,1'-biphenyla-3-ylamino)carbonyl]amino}benzoate

[0624] 23.4 mg, LC-MS: purity 96%, Rt = 4.06 mjn, m/z: 529 $[M+H]^+$

Example 347

Methyl 2-(benzhydryloxy)-5-{[(1,1'-biphenyla-2-ylamino)carbonyl]amino}benzoate

[0625] 28.5 mg, LC-MS: purity 87%, Rt = 4.00 mjn, m/z: 529 $[M+H]^+$

Example 348

Methyl 2-(benzhydryloxy)-5-({[(3-bromophenyl)amino]carbonyl}amino)benzoate

[0626] 30.7 mg, LC-MS: purity 87%, Rt = 3.94 mjn, m/z: 553 $[M+Na]^+$

Example 349

Methyl 2-(benzhydryloxy)-5-({[(2-bromophenyl)amino]carbonyl}amino)benzoate

[0627] 19.1 mg, LC-MS: purity 82%, Rt = 3.90 mjn, m/z: 553 $[M+Na]^+$

Example 350

Methyl 2-(benzhydryloxy)-5-({[(4-bromophenyl)amino]carbonyl}amino)benzoate

[0628] 25.5 mg, LC-MS: purity 98%, Rt = 3.93 mjn, m/z: 553 $[M+Na]^+$

Example 351

Methyl 5-[({[4-(aminosulfonyl)phenyl]amino}carbonyl)amino]-2-(benzhydryloxy)benzoate

[0629] 4.3 mg, LC-MS: purity 83%, Rt = 3.26 mjn, m/z: 554 $[M+Na]^+$

Example 352

Methyl 2-(benzhydryloxy)-5-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]benzoate

[0630] 24.7 mg, LC-MS: purity 99%, Rt = 4.00 mjn, m/z: 559 $[M+Na]^+$

Example 353

Methyl 2-(benzhydryloxy)-5-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]benzoate

[0631] 20.6 mg, LC-MS: purity 99%, Rt = 4.00 mjn, m/z: 561 $[M+Na]^+$

Example 354

Methyl 2-(benzhydryloxy)-5-[({[4-(2-ethoxy-2-oxoethyl)phenyl]amino}carbonyl)amino]benzoate

[0632] 27.0 mg, LC-MS: purity 99%, Rt = 3.74 mjn, m/z: 539 $[M+H]^+$

Example 355

Methyl 2-(benzhydryloxy)-5-[({[4-(pentyloxy)phenyl]amino}carbonyl)amino]benzoate

[0633] 30.5 mg, LC-MS: purity 99%, Rt = 4.21 mjn, m/z: 539 $[M+H]^+$

Example 356

Methyl 2-(benzhydryloxy)-5-({[(6-methoxy-1,3-benzothiazol-2-yl)amino]carbonyl}amino)benzoate

[0634] 23.8 mg, LC-MS: purity 91%, Rt = 3.78 mjn, m/z: 540 $[M+H]^+$

Example 357

Methyl 2-(benzhydryloxy)-5-[({[2-methoxy-4-(methoxycarbonyl)phenyl]amino}carbonyl)amino]benzoate

[0635] 23.6 mg, LC-MS: purity 99%, Rt = 3.74 mjn, m/z: 541 $[M+H]^+$

Example 358

Methyl 2-(benzhydryloxy)-5-({[(4-benzylphenyl)amino]carbonyl}amino)benzoate

[0636] 34.6 mg, LC-MS: purity 90%, Rt = 4.10 mjn, m/z: 543 $[M+H]^+$

Example 359

Methyl 5-({[(2-anilin ophenyl)amino]carbonyl}amino)-2-(benzhydryloxy)benzoate

[0637] 28.8 mg, LC-MS: purity 99%, Rt = 4.00 mjn, m/z: 544 $[M+H]^+$

Example 360

Methyl 2-(benzhydryloxy)-5-({[(3-phenoxyphenyl)amino]carbonyl}amino)benzoate

[0638] 33.1 mg, LC-MS: purity 83%, Rt = 4.07 mjn, m/z: 545 $[M+H]^+$

Example 361

Methyl 2-(benzhydryloxy)-5-({[(4-phenoxyphenyl)amino]carbonyl}amino)benzoate

[0639] 34.0 mg, LC-MS: purity 88%, Rt = 4.04 mjn, m/z: 545 $[M+H]^+$

Example 362

Methyl 2-(benzhydryloxy)-5-({[(2-phenoxyphenyl)amino]carbonyl}amino)benzoate

[0640] 25.3 mg, LC-MS: purity 99%, Rt = 4.14 mjn, m/z: 545 $[M+H]^+$

Example 363

Methyl 2-(benzhydryloxy)-5-({[(3,4,5-trimethoxyphenyl)amino]carbonyl}amino)benzoate

[0641] 31.0 mg, LC-MS: purity 98%, Rt = 3.53 mjn, m/z: 543 $[M+H]^+$

Example 364

Methyl 2-(benzhydryloxy)-5-[({[4-(4-methylpiperazin-1-yl)phenyl]amino}carbonyl)amino]benzoate

[0642] 32.9 mg, LC-MS: purity 98%, Rt = 2.77 mjn, m/z: 551 $[M+H]^+$

Example 365

Methyl 2-(benzhydryloxy)-5-({[(9-oxo-9H-fluoren-2-yl)amino]carbonyl)amino)benzoate

[0643] 26.8 mg, LC-MS: purity 89%, Rt = 3.95 mjn, m/z: 555 $[M+H]^+$

Example 366

Methyl 2-(benzhydryloxy)-5-{[({4-[(E)-2-phenylethenyl]phenyl}amino)carbonyl]amino}benzoate

[0644] 22.5 mg, LC-MS: purity 99%, Rt = 4.20 mjn, m/z: 555 $[M+H]^+$

Example 367

Methyl 2-(benzhydryloxy)-5-({[(4-benzoylphenyl)amino]carbonyl}amino)benzoate

[0645] 14.3 mg, LC-MS: purity 98%, Rt = 3.91 mjn, m/z: 579 $[M+Na]^+$

Example 368

Methyl 2-(benzhydryloxy)-5-({[(4-methoxy-1,1'-biphenyla-3-yl)amino]carbonyl}amino)benzoate

[0646] 24.3 mg, LC-MS: purity 100%, Rt = 4.18 mjn, m/z: 559 $[M+H]^+$

Example 369

Methyl 2-(benzhydryloxy)-5-[({[3-(benzyloxy)phenyl]amino}carbonyl)amino]benzoate

[0647] 29.2 mg, LC-MS: purity 81%, Rt = 4.05 mjn, m/z: 559 $[M+H]^+$

Example 370

Methyl 2-(benzhydryloxy)-5-[({[4-(heptyloxy)phenyl]amino}carbonyl)amino]benzoate

[0648] 22.8 mg, LC-MS: purity 97%, Rt = 4.49 mjn, m/z: 567 $[M+H]^+$

Example 371

Dimethyl 5-[({[4-(benzhydryloxy)-3-(methoxycarbonyl)phenyl]amino}carbonyl)amino]isophthalate

[0649] 26.1 mg, LC-MS: purity 98%, Rt = 3.76 mjn, m/z: 569 $[M+H]^+$

Example 372

Methyl 2-(benzhydryloxy)-5-({[(4'-nitro-1,1'-biphenyla-4-yl)amino]carbonyl}amino)benzoate

[0650] 24.2 mg, LC-MS: purity 87%, Rt = 4.04 mjn, m/z: 596 $[M+Na]^+$

Example 373

Methyl 2-(benzhydryloxy)-5-({[(1-benzyl-1H-benzoimidazol-2-yl)amino]carbonyl}amino)benzoate

[0651] 25.4 mg, LC-MS: purity 96%, Rt = 3.57 mjn, m/z: 583 $[M+H]^+$

Example 374

Methyl 2-(benzhydryloxy)-5-{[({4-[(E)-2-(4-methoxyphenyl)ethenyl]phenyl}amino)carbonyl]amino}benzoate

[0652] 23.0 mg, LC-MS: purity 99%, Rt = 4.14 mjn, m/z: 585 $[M+H]^+$

Example 375

Methyl 2-(benzhydryloxy)-5-[({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)amino]benzoate

[0653] 17.3 mg, LC-MS: purity 93%, Rt = 4.27 mjn, m/z: 611 $[M+Na]^+$

Example 376

Methyl 2-(benzhydryloxy)-5-[({[4-(benzyloxy)phenyl]amino}carbonyl)amino]benzoate

[0654] 29.9 mg, LC-MS: purity 97%, Rt = 3.99 mjn, m/z: 559 $[M+H]^+$

Example 377

Methyl 2-(benzhydryloxy)-5-{[({4-[(phenylsulfonyl)amino]phenyl}amino)carbonyl]amino}benzoate 34.5 mg, LC-MS: purity 99%, Rt = 3.71 mjn, m/z: 622 $[M+H]^+$

Synthetic method of amide derivatives by combinatorial synthesis

[0655] The compounds of Examples 378 to 425 were synthesized as described below.

[0656] To a mixed solution of 5-(anilinocarbonylamino)-2-benzhydryloxy benzoate (0.0684 mmol), 1-hydroxy-7-aza-benzotriazole (0.0821 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.1026 mmol) in DMF (0.3 mL) and dichloromethane (0.7 mL) was added amine (0.0821 mmol), the mixture was stirred at room temperature for 2 hours, and water and dichloromethane were added to the mixture. The layer of dichloromethane was separated with PTFE filter (1μm, Whatman Inc.), and concentrated with Dry Thermo-unit PTU-1C. The residue was purified with preparative HPLC made by Gilson Inc. (PLRP-S column 5 μm 100 A, 50 x 25 mm, 40% to 100% aqueous solution of acetonitrile). The resulting compound was analyzed by LC MASS made by Gilson Inc. (Shiseido capsule pack C18 2 x 5 cm, λ = 220 nm, temperature 40°C, A liquid 0.05% trifluoroacetic acid solution: B liquid acetonitrile: 10 to 95% B liquid (for 4

minutes) 95% B liquid (for 1.5 minutes), electrospray ionization mass spectrum).

Example 378

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N,N-dipropyl benzamide

[0657] 23.5 mg, LC-MS: purity 97%, Rt = 3.88 mjn, m/z: 522 $[M+H]^+$

Example 379

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-methyl-N-(1-naphthylmethyl)benzamide

[0658] 30.4 mg, LC-MS: purity 97%, Rt = 4.01 mjn, m/z: 592 $[M+H]^+$

Example 380

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl benzamide

[0659] 31.0 mg, LC-MS: purity 97%, Rt = 3.61 mjn, m/z: 616 $[M+H]^+$

Example 381

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N,N-bis(2-methoxyethyl)benzamide

[0660] 27.5 mg, LC-MS: purity 96%, Rt = 3.46 mjn, m/z: 554 $[M+H]^+$

Example 382

N-[4-(Benzhydryloxy)-3-(piperidin-1-ylcarbonyl)phenyl]-N'-phenylurea

[0661] 26.5 mg, LC-MS: purity 97%, Rt = 3.65 mjn, m/z: 506 $[M+H]^+$

Example 383

N-{4-(Benzhydryloxy)-3-[(2,6-dimethylmorpholin-4-yl)carbonyl]phenyl}-N'-phenylurea

[0662] 27.4 mg, LC-MS: purity 98%, Rt = 3.54 mjn, m/z: 536 $[M+H]^+$

Example 384

N-[4-(Benzhydryloxy)-3-(3,4-dihydroisoquinolin-2 (1H)-ylcarbonyl)phenyl]-N'-phenylurea

[0663] 25.0 mg, LC-MS: purity 99%, Rt = 3.79 mjn, m/z: 554 $[M+H]^+$

Example 385

1-[5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)benzoyl]piperidin-4-carboxamide

[0664] 26.7 mg, LC-MS: purity 98%, Rt = 2.94 mjn, m/z: 549 $[M+H]^+$

Example 386

N-(4-(Benzhydryloxy)-3-{[4-(2-hydroxyethyl)piperidin-1-yl]carbonyl}phenyl)-N'-phenylurea

[0665] 24.4 mg, LC-MS: purity 99%, Rt = 3.15 mjn, m/z: 550 $[M+H]^+$

Example 387

N-[4-(Benzhydryloxy)-3-(thiomorpholin-4-ylcarbonyl)phenyl]-N'-phenylurea

[0666] 26.8 mg, LC-MS: purity 99%, Rt = 3.57 mjn, m/z: 524 $[M+H]^+$

Example 388

N-{4-(Benzhydryloxy)-3-[(4-benzylpiperidin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0667] 27.1 mg, LC-MS: purity 99%, Rt = 4.09 mjn, m/z: 596 $[M+H]^+$

Example 389

N-{1-[5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)benzoyl]pyrrolidin-3-yl}acetamide

[0668] 23.0 mg, LC-MS: purity 99%, Rt = 2.97 mjn, m/z: 549 $[M+H]^+$

Example 390

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-cyclohexyl-N-methyl benzamide

[0669] 27.1 mg, LC-MS: purity 98%, Rt = 3.92 mjn, m/z: 534 $[M+H]^+$

Example 391

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-benzyl-N-methyl benzamide

[0670] 28.4 mg, LC-MS: purity 100%, Rt = 3.79 mjn, m/z: 542 $[M+H]^+$

Example 392

Ethyl N-[5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)benzoyl]-N-benzyl-beta-alanate

[0671] 25.7 mg, LC-MS: purity 97%, Rt = 3.89 mjn, m/z: 628 $[M+H]^+$

Example 393

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-ethyl-N-(2-methoxyethyl)benzamide

[0672] 28.1 mg, LC-MS: purity 98%, Rt = 3.51 mjn, m/z: 524 $[M+H]^+$

Example 394

N-[3-(Azepan-1-ylcarbonyl)-4-(benzhydryloxy)phenyl]-N'-phenylurea

[0673] 27.8 mg, LC-MS: purity 98%, Rt = 3.75 mjn, m/z: 520 $[M+H]^+$

Example 395

N-{4-(Benzhydryloxy)-3-[(3,5-dimethylpiperidin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0674] 26.8 mg, LC-MS: purity 99%, Rt = 3.95 mjn, m/z: 534 $[M+H]^+$

Example 396

N-[4-(Benzhydryloxy)-3-(octahydroisoquinolin-2 (1H)-ylcarbonyl)phenyl]-N'-phenylurea

[0675] 27.5 mg, LC-MS: purity 99%, Rt = 4.11 mjn, m/z: 560 $[M+H]^+$

Example 397

Ethyl 1-[5-[(anilinocarbonyl)amino]-2-(benzhydryloxy)benzoyl]piperidin-4 carbonate

[0676] 22.5 mg, LC-MS: purity 98%, Rt = 3.60 mjn, m/z: 578 $[M+H]^+$

Example 398

N-{4-(Benzhydryloxy)-3-[(4-hydroxypiperidin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0677] 25.1 mg, LC-MS: purity 99%, Rt = 3.05 mjn, m/z: 522 $[M+H]^+$

Example 399

N-{4-(Benzhydryloxy)-3-[(2-{[(2,6-dimethylphenyl)amino]methyl}pyrrolidin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0678] 29.7 mg, LC-MS: purity 100%, Rt = 3.13 mjn, m/z: 625 $[M+H]^+$

Example 400

N-(4-(Benzhydryloxy)-3-{[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]carbonyl}phenyl)-N'-phenylurea

[0679] 24.4 mg, LC-MS: purity 99%, Rt = 3.71 mjn, m/z: 632 $[M+H]^+$

Example 401

N-{1-[5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)benzoyl]pyrrolidin-3-yl}-N-ethyl acetamide

[0680] 26.7 mg, LC-MS: purity 99%, Rt = 3.18 mjn, m/z: 577 $[M+H]^+$

Example 402

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-[2-(dimethylamino)ethyl]-N-methyl benzamide

[0681] 28.6 mg, LC-MS: purity 99%, Rt = 2.57 mjn, m/z: 523 $[M+H]^+$

Example 403

5-[(Aanilinocarbonyl)amino]-2-(benzhydryloxy)-N-(1-benzylpyrrolidin-3-yl)-N-methyl benzamide

[0682] 31.4 mg, LC-MS: purity 99%, Rt = 2.86 mjn, m/z: 611 $[M+H]^+$

Example 404

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-ethyl-N-(pyridin-4-ylmethyl)benzamide

[0683] 29.6 mg, LC-MS: purity 99%, Rt = 2.66 mjn, m/z: 557 $[M+H]^+$

Example 405

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N,N-bis(pyridin-3-ylmethyl)benzamide

[0684] 29.3 mg, LC-MS: purity 98%, Rt = 2.33 mjn, m/z: 620 $[M+H]^+$

Example 406

N-{4-(Benzhydryloxy)-3-[(4-ethylpiperazin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0685] 24.4 mg, LC-MS: purity 98%, Rt = 2.55 mjn, m/z: 535 $[M+H]^+$

Example 407

{4-[5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)benzoyl]piperazin-1-yl}ethyl acetate

[0686] 22.9 mg, LC-MS: purity 99%, Rt = 2.71 mjn, m/z: 593 $[M+H]^+$

Example 408

N-{4-(Benzhydryloxy)-3-[(4-benzylpiperazin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0687] 29.0 mg, LC-MS: purity 99%, Rt = 2.78 mjn, m/z: 597 $[M+H]^+$

Example 409

N-{4-(Benzhydryloxy)-3-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0688] 26.0 mg, LC-MS: purity 98%, Rt = 2.61 mjn, m/z: 584 $[M+H]^+$

Example 410

N-{4-(Benzhydryloxy)-3-[(4-benzhydrylpiperazin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0689] 37.4 mg, LC-MS: purity 98%, Rt = 3.15 mjn, m/z: 673 $[M+H]^+$

Example 411

N-{4-(Benzhydryloxy)-3-[(4-phenylpiperazin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0690] 23.5 mg, LC-MS: purity 98%, Rt = 3.66 mjn, m/z: 583 $[M+H]^+$

Example 412

N-(4-(Benzhydryloxy)-3-{[4-(2-methoxyphenyl)piperazin-1-yl]carbonyl}phenyl)-N'-phenylurea

[0691] 30.4 mg, LC-MS: purity 96%, Rt = 3.37 mjn, m/z: 613 $[M+H]^+$

Example 413

N-[4-(Benzhydryloxy)-3-(1,4'-bipiperidin-1'-ylcarbonyl)phenyl]-N'-phenylurea

[0692] 28.1 mg, LC-MS: purity 89%, Rt = 2.62 mjn, m/z: 589 $[M+H]^+$

Example 414

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-methyl-N-(1-methylpyrrolidin-3-yl)benzamide

[0693] 28.3 mg, LC-MS: purity 95%, Rt = 2.61 mjn, m/z: 535 $[M+H]^+$

Example 415

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-benzyl-N-(1-benzylpyrrolidin-3-yl)benzamide

[0694] 35.0 mg, LC-MS: purity 98%, Rt = 3.14 mjn, m/z: 687 $[M+H]^+$

Example 416

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N,N-bis(pyridin-2-ylmethyl)benzamide

[0695] 33.6 mg, LC-MS: purity 96%, Rt = 2.73 mjn, m/z: 620 $[M+H]^+$

Example 417

N-{4-(Benzhydryloxy)-3-[(4-methyl-1,4-diazepan-1-yl)carbonyl]phenyl}-N'-phenylurea

[0696] 27.2 mg, LC-MS: purity 97%, Rt = 2.53 mjn, m/z: 535 $[M+H]^+$

Example 418

N-(4-(Benzhydryloxy)-3-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}phenyl)-N'-phenylurea

[0697] 28.0 mg, LC-MS: purity 99%, Rt = 2.47 mjn, m/z: 551 $[M+H]^+$

Example 419

N-(4-(Benzhydryloxy)-3-{[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}phenyl)-N'-phenylurea

[0698] 30.6 mg, LC-MS: purity 100%, Rt = 2.78 mjn, m/z: 641 $[M+H]^+$

Example 420

N-{4-(Benzhydryloxy)-3-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0699] 30.9 mg, LC-MS: purity 97%, Rt = 3.34 mjn, m/z: 585 $[M+H]^+$

Example 421

N-[4-(Benzhydryloxy)-3-({4-[(2E)-3-phenylpropa-2-enyl]piperazin-1-yl}carbonyl)phenyl]-N'-phenylurea

[0700] 32.9 mg, LC-MS: purity 97%, Rt = 2.93 mjn, m/z: 623 $[M+H]^+$

Example 422

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-benzyl-N-[2-(dimethylamino)ethyl]benzamide

[0701] 25.7 mg, LC-MS: purity 97%, Rt = 2.89 mjn, m/z: 599 $[M+H]^+$

Example 423

5-[(Anilinocarbonyl)amino]-2-(benzhydryloxy)-N-methyl-N-(1-methylpiperidin-4-yl)benzamide

[0702] 28.0 mg, LC-MS: purity 98%, Rt = 2.55 mjn, m/z: 549 $[M+H]^+$

Example 424

N-(4-(Benzhydryloxy)-3-{[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}phenyl)-N'-phenylurea

[0703] 26.2 mg, LC-MS: purity 95%, Rt = 2.79 mjn, m/z: 575 $[M+H]^+$

Example 425

N-{4-(Benzhydryloxy)-3-[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]phenyl}-N'-phenylurea

[0704] 7.0 mg, LC-MS: purity 89%, Rt = 2.62 mjn, m/z: 575 $[M+H]^+$

[0705] According to the same method as Example 236, the following compounds were synthesized.

Example 426

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-(dipyridin-2-ylmethoxy)benzoate

(1) Methyl 2-(dipyridin-2-ylmethoxy)-5-nitrobenzoate

[0706] ^{1}H-NMR ($CDCl_3$) δ; 4.02 (3H, s), 6.68 (1H, s), 6.98 to 7.81 (9H, m), 8.22 (1H, d, J = 2.8, 9.0 Hz), 8.77 (2H, d, J = 2.8 Hz)

(2) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-(dipyridin-2-ylmethoxy)benzoate

[0707] ^{1}H-NMR ($CDCl_3$) δ; 3.79 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 6.50 (1H, s), 6.68 to 7.85 (13H, m), 7.97 (1H, s), 8.51 (2H, d, J = 4.8 Hz)

Example 427

Methyl 2-[bis(4-methylphenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 2-[bis(4-methylphenyl)methoxy]-5-nitrobenzoate

[0708] ^{1}H-NMR ($CDCl_3$) δ; 2.32 (6H, s), 3.97 (3H, s), 6.35 (1H, s), 7. 02 (1H, d = 9. 0 Hz), 7.15 (4H, d, J = 8. 0 Hz), 7.35 (4H, d, J = 8.0 Hz), 8.16 (1H, dd, J = 3.0, 9.0 Hz), 8.70 (1H, d, J = 3.0 Hz)

(2) Methyl 2-[bis(4-methylphenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0709] ^{1}H-NMR ($CDCl_3$) δ; 2.28 (6H, s), 3.81 (3H, s), 3.82 (3H, s), 3.86 (3H, s), 6.15 (1H, s), 6.68 to 7.42 (15H, m), 7.58 (1H, d, J = 2.8 Hz)

Example 428

Methyl 2-[bis(4-chlorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 2-[bis(4-chlorophenyl)methoxy]-5-nitrobenzoate

[0710] ^{1}H-NMR ($CDCl_3$) δ; 4.04 (3H, s), 6.36 (1H, s), 6.97 (1H, d, J = 7.6 Hz), 7.34 (4H, d, J = 10.8 Hz), 7.43 (4H, d, J = 10.8 Hz), 8.20 (1H, dd, J = 2.4, 7.6 Hz), 8.73 (1H, d, J = 2.4 Hz)

(2) Methyl 2-[bis(4-chlorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0711] ^{1}H-NMR (DMSO-d6) δ; 3.70 (3H, s), 3.72 (3H, s), 3.89 (3H, s), 6.69 (1H, s), 6.85 to 7.59 (13H, m), 7.89 (1H, d, J = 2.4 Hz), 8.45 (1H, s), 8.53 (1H, s)

Example 429

Methyl 2-[bis(4-chlorophenyl)methoxy]-5-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0712] ^{1}H-NMR (DMSO-d6) δ; 3.72 (3H, s), 3.89 (3H, s), 6.53 to 7.59 (15H, m), 7.89 (1H, d, J = 2.8 Hz), 8.60 (1H, s), 8.62 (1H, s)

Example 430

Methyl 2-[bis(4-chlorophenyl)methoxy]-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0713] ^{1}H-NMR (DMSO-d6) δ; 3.71 (3H, s), 3.89 (3H, s), 6.68 (1H, s), 6.84 to 7.59 (14H, m), 7.89 (1H, d, J = 2.4 Hz), 8.41 (1H, s), 8.54 (1H, s)

Example 431

Methyl 2-[bis(4-methylphenyl)methoxy]-5-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0714] ^{1}H-NMR ($CDCl_3$) δ; 2.26 (6H, s), 3.62 (3H, s), 3.81 (3H, s), 6.07 (1H, s), 6.69 to 7.57 (17H, m)

Example 432

Methyl 2-[bis(4-methylphenyl)methoxy]-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0715] ^{1}H-NMR ($CDCl_3$) δ; 2.28 (6H, s), 3.76 (3H, s), 3.86 (3H, s), 6.15 (1H, s), 6.56 (1H, s), 6.63 (1H, s), 6.81 to 7.41 (14H, m), 7.58 (1H, d, J = 2.8 Hz)

Example 433

Methyl 5-[(anilinocarbonyl)amino]-2-[bis(4-methylphenyl)methoxy]benzoate

[0716] ^{1}H-NMR ($CDCl_3$) δ; 2.28 (6H, s), 3.85 (3H, s), 6.13 (1H, s), 6.80 to 7.36 (17H, m), 7.59 (1H, d, J = 2.4 Hz)

Example 434

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate

(1) Methyl 2-[bis(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0717] ^{1}H-NMR ($CDCl_3$) δ; 3.98 (3H, s), 6.39 (1H, s), 6.99 (1H, d, J = 9.2 Hz), 7.04 to 7.49 (8H, m), 8.20 (1H, dd, J = 2.8, 9.2 Hz), 8.73 (1H, d, J = 2.8 Hz)

(2) Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0718] ^{1}H-NMR ($CDCl_3$) δ; 3.71 (3H, s), 3.82 (3H, s), 6.13 (1H, s), 6.58 to 7.42 (16H, m), 7.60 (1H, d, J = 2.8 Hz)

Example 435

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate

[0719] ^{1}H-NMR ($CDCl_3$) δ; 3.76 (3H, s), 3.84 (3H, s), 6.16 (1H, s), 6.57 to 7.43 (16H, m), 7.60 (1H, d, J = 2.8 Hz)

Example 436

Methyl 5-[(anilinocarbonyl)amino]-2-[bis(4-fluorophenyl)methoxy]benzoate

[0720] ^{1}H-NMR ($CDCl_3$) δ; 3.83 (3H, s), 6.14 (1H, s), 6.74 (1H, d, J = 9.2 Hz), 6.90 to 7.42 (16H, m), 7.62 (1H, d, J = 2.8 Hz)

Example 437

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0721] ^{1}H-NMR ($CDCl_3$) δ; 3.70 (3H, s), 3.72 (3H, s), 3.88 (3H, s), 6.67 (1H, s), 6.84 (2H, s), 7.06 to 7.61 (11H, m), 7.87 (1H, d, J = 2.8 Hz), 8.44 (1H, s), 8.52 (1H, s).

Example 438

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-{[({4-[(2,2-dimethylpropanoyl)oxy]-3-methoxyphenyl}amino)carbonyl]amino} benzoate

[0722] A solution (10 mL) of 4-[(2,2-dimethylpropanoyl)oxy]-3-methoxy benzoate (253 mg, 1.00 mmol) and triethyl amine (0.294 mL, 2.10 mmol), diphenylphosphoryl azide (0.230 mL, 1.05 mmol) in toluene was stirred at room temperature for 30 minutes at 93°C for 1.5 hours, and the reaction solution was cooled to room temperature. Methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (259 mg, 0.700 mmol) was added thereto and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water, extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 3:2), to obtain the titled compound as powder. 433 mg (100%)

^{1}H-NMR (DMSO-d6) δ; 1.29 (9H, s), 3.72 (3H, s), 3.89 (3H, s), 6.68 (1H, s), 6.91 to 7.61 (13H, m), 7.89 (1H, d, J = 3.2 Hz), 8.61 (1H, s), 8.68 (1H, s)

Example 439

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(methylthio)phenyl]amino}carbonyl)amino]benzoate

[0723] To a solution (15 mL) of methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (999 mg, 2.50 mmol) in THF was added 4-methylthiophenyl isocyanate (0.342 mL, 2.50 mmol), and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water, extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 3:2), to obtain the titled compound as a solid. 1.35 g (98%)

^{1}H-NMR (DMSO-d6) δ; 2.43 (3H, s), 3.89 (3H, s), 6.68 (1H, s), 7.07 to 7.61 (14H, m), 7.87 (1H, d, J = 2.4 Hz), 8.60 (1H, s), 8.63 (1H, s)

Example 440

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({(4-(methylsulfinyl)phenyl]amino}carbonyl)amino]benzoate

[0724] To a solution (10 mL) of methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(methylthio)phenyl]amino}carbonyl) amino]benzoate (268 mg, 0.500 mmol) in methylene chloride was added m-chloroperbenzoate (70%, 123 mg, 0.500 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hours. The solvent was distilled off under reduced pressure, and the residue was added to an aqueous solution of sodium bicarbonate, and was extracted with ethyl acetate-THF (2:1). The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (methanol:ethyl acetate = 1:20), to obtain the titled compound as a solid. 159 mg (57%)

^{1}H-NMR (DMSO-d6) δ; 2.70 (3H, s), 3.89 (3H, s), 6.70 (1H, s), 7.09 to 7.64 (14H, m), 7.90 (1H, d, J = 2.0 Hz), 8.73 (1H, s), 8.96 (1H, s)

Example 441

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(methylsulfonyl)phenyl]amino}carbonyl)amino]benzoate

[0725] To a solution (10 mL) of methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(methylthio)phenyl]amino}carbonyl) amino]benzoate (268 mg, 0.500 mmol) in methylene chloride was added m-chloroperbenzoate (70%, 247 mg, 1.00 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure, and the residue was added to an aqueous solution of sodium bicarbonate, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane: ethyl acetate = 3:1), to obtain the titled compound as a solid. 261 mg (84%)

^{1}H-NMR (DMSO-d6) δ; 3.15 (3H, s), 3.89 (3H, s), 6.70 (1H, s), 7.10 to 7.81 (14H, m), 7.91 (1H, d, J = 2.8 Hz), 8.80 (1H, s), 9.18 (1H, s)

Example 442

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(4-ethoxy-3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0726] From 4-ethoxy-3-methoxy benzoate and methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate was synthesized the titled compound in the same manner as Example 438.

^{1}H-NMR (DMSO-d6) δ; 1.29 (3H, t, J = 7.2 Hz), 3.73 (3H, s), 3.89 (3H, s), 3.94 (2H, q, J = 7.2 Hz), 6.68 (1H, s), 6.82 to 7.61 (13H, m), 7.87 (1H, d, J = 2.8 Hz), 8.44 (1H, s), 8.52 (1H, s)

Example 443

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[3-methoxy-4-(methoxymethoxy)phenyl]amino}carbonyl)amino]benzoate

[0727] From 3-methoxy-4-(methoxymethoxy)benzoate and methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate was synthesized the titled compound in the same manner as Example 438.

^{1}H-NMR (DMSO-d6) δ; 3.39 (3H, s), 3.75 (3H, s), 3.89 (3H, s), 5.04 (2H, s), 6.68 (1H, s), 6.80 to 7.61 (13H, m), 7.87 (1H, d, J = 3.2 Hz), 8.52 (1H, s), 8.54 (1H, s)

Example 444

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-{[({3-methoxy-4-[(methylsulfonyl)oxy]phenyl}amino)carbonyl]amino} benzoate

[0728] From 3-methoxy-4-[(methylsulfonyl)oxy]benzoate and methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate was synthesized the titled compound in the same manner as Example 438.

^{1}H-NMR (DMSO-d6) δ; 3.29 (3H, s), 3.81 (3H, s), 3.89 (3H, s), 6.69 (1H, s), 6.90 to 7.61 (13H, m), 7.88 (1H, d, J = 2.4 Hz), 8.66 (1H, s), 8.82 (1H, s)

Example 445

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(2-ethoxy-2-oxoethoxy)-3-methoxyphenyl]amino}carbonyl)amino] benzoate

[0729] A solution (30 mL) of 4-hydroxy-3-methoxybenzaldehyde (4.57 g, 30.0 mmol), potassium carbonate (4.98 g, 36.0 mmol) and bromoethyl acetate (4.00 mL, 36.0 mmol) in DMF was stirred at room temperature for 3 hours, and the reaction solution was poured into water and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. To the residue (2.39 g) were added acetic acid (12 mL) and sulfamic acid (1.31 g, 13.5 mmol) and to this solution was added a solution of sodium chlorite (1.47 g, 13.0 mmol) in water (3 mL). The mixture was stirred at room temperature for 30 minutes, water (50 mL) was added thereto, and the solid were collected. A solution of this solid (255 mg), triethyl amine (0.150 mL, 1.05 mmol) and diphenylphosphoryl azide (0.230 mL, 1.05 mmol) in toluene (10 mL) was stirred at room temperature for 15 minutes and at 93°C for 1.5 hours, and the reaction solution was cooled to room temperature. Methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (259 mg, 0.700 mmol) was added thereto, and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water, extracted with ethyl acetate,

and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as powder. 436 mg (70.3%)

^{1}H-NMR (DMSO-d6) δ; 1.21 (3H, t, J = 7.2 Hz), 3.75 (3H, s), 3.89 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.66 (2H, s), 6.68 (1H, s), 6.80 to 7.60 (13H, m), 7.87 (1H, d, J = 2.4 Hz), 8.49 (1H, s), 8.54 (1H, s)

Example 446

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-{[({4-[(ethoxycarbonyl)oxy]-3-methoxyphenyl}amino)carbonyl]amino} benzoate

[0730] From 4-[(ethoxycarbonyl)oxy]-3-methoxy benzoate and methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate was synthesized the titled compound in the same manner as Example 438.

^{1}H-NMR (DMSO-d6) δ; 1.27 (3H, t, J = 7.2 Hz), 3.76 (3H, s), 3.89 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 6.69 (1H, s), 6.87 to 7.61 (13H, m), 7.89 (1H, d, J = 2.4 Hz), 8.63 (1H, s), 8.73 (1H, s)

Example 447

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(4-hydroxy-3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0731] A solution (2 mL) of methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[({4-[(ethoxycarbonyl)oxy]-3-methoxyphenyl} amino)carbonyl]amino}benzoate (122 mg, 0.200 mmol) and potassium carbonate (28 mg, 0.200 mmol) in methanol was stirred under ice-cooling for 15 minutes and at room temperature for 1.5 hours, the reaction solution was poured into water and was extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:2), to obtain the titled compound as oil. 88.0 mg (82.2%)

^{1}H-NMR (DMSO-d6) δ; 3.73 (3H, s), 3.88 (3H, s), 6.65 to 7.61 (14H, m), 7.87 (1H, d, J = 2.4 Hz), 8.32 (1H, s), 8.48 (1H, s), 8.57 (1H, s)

Example 448

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(4-isopropoxy-3-methoxyphenyl)amino]carbonyl}amino)benzoate

[0732] From methyl 4-isopropoxy-3-methoxy benzoate and 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate was synthesized the titled compound in the same manner as Example 438.

^{1}H-NMR (DMSO-d6) δ; 1.21 (6H, d, J = 6.0 Hz), 3.72 (3H, s), 3.89 (3H, s), 4.36 to 4.39 (1H, m), 6.68 (1H, s), 6.81 to 7.61 (13H, m), 7.87 (1H, d, J = 2.0 Hz), 8.46 (1H, s), 8.53 (1H, s)

Example 449

Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-(dithien-2-ylmethoxy)benzoate

[0733] According to the same method as Example 236 was synthesized the titled compound.

(1) Methyl 2-(dithien-2-ylmethoxy)-5-nitrobenzoate

[0734] ^{1}H-NMR ($CDCl_3$) δ; 4.02 (3H, s), 6.36 (1H, s), 6.85 to 7.26 (6H, m), 8.26 (1H, d, J = 2.4 Hz), 8.73 (1H, d, J = 2.4 Hz), 11.93 (1H, s)

(2) Methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-(dithien-2-ylmethoxy)benzoate

[0735] ^{1}H-NMR (DMSO-d6) δ; 3.70 (3H, s), 3.73 (3H, s), 3.92 (3H, s), 6.29 (1H, s), 6.84 to 7.45 (10H, m), 8.11 (1H, d, J = 2.0 Hz), 8.26 (1H, s), 8.61 (1H, s), 10.74 (1H, s)

Example 450

Methyl 5-[({[4-(2-aminoethoxy)-3-methoxyphenyl]amino}carbonyl)amino]-2-[bis(4-fluorophenyl)methoxy]benzoate

(1) 4-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethoxy]-3-methoxy benzoate

[0736] A mixture of 4-hydroxy-3-methoxybenzaldehyde (4.57 g, 30.0 mmol), 1,2-dibromoethane (20 mL), 10% tetrabutylammonium hydroxide solution (12 mL), potassium hydroxide (12 g) and water (18 mL) was stirred at 53°C for 2 hours. After cooling, the organic layer was collected, and the aqueous layer was extracted with methylene chloride. The organic layer was combined with the extracted solution, washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from hexane and ether. These crystals (2.59 g) and potassium phthalimide (2.04 g, 11.0 mmol) were suspended in DMF (10 mL), the mixture was stirred at 57°C for 2 hours, and the reaction solution was poured into ice-water to obtain crystals. To these crystals (2.93 g) were added acetic acid (12 mL) and sulfamic acid (1.18 g, 12.2 mmol) and to this solution was added a solution of sodium chlorite (1.32 g, 11.7 mmol) in water (3 mL). The mixture was stirred for 1 hour at room temperature, and water (50 mL) was added thereto, to obtain the titled compound as a solid. 2.86 g (93%)

^{1}H-NMR (DMSO-d6) δ; 3.67 (3H, s), 3.98 (2H, t, J = 6.0 Hz), 4.31 (2H, t, J = 6.0 Hz), 7.07 to 7.91 (7H, m)

(2) 3-Methoxy-4-{2-[(trifluoroacetyl)amino]ethoxy}benzoate

[0737] A suspension of 4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethoxy]-3-methoxy benzoate (6.32 g, 18.5 mmol), methylhydrazine (3.92 mL, 74.0 mmol) and ethanol (120 mL) was heated to reflux for 4 hours. After cooling, the precipitated crystals were collected, washed with small amount of ethanol, and dried. These crystals (1.33 g) were suspended in methylene chloride (10 mL), trifluoroacetic anhydride (3 mL, 21.7 mmol) was added to the suspension under ice-cooling, and the mixture was stirred at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure, and the residue was poured into ice-water, and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was extracted with saturated aqueous solution of sodium bicarbonate. This sodium bicarbonate solution was acidified with 1 N hydrochloric acid, and further extracted with ethyl acetate. The extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 910 mg (47%)

^{1}H-NMR (DMSO-d6) δ; 3.57 to 3.62 (2H, m), 3.80 (3H, s), 4.18 (2H, t, J = 5.6 Hz), 7.08 (1H, d, J = 8.4 Hz), 7.46 (1H, s), 7.54 (1H, d, J = 8.4 Hz), 9.95 (1H, s), 12.69 (1H, s)

(3) Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3-methoxy-4-{2-[(trifluoroacetyl)amino]ethoxy}phenyl)amino]carbonyl} amino) benzoate

[0738] A solution (6 mL) of 3-methoxy-4-{2-[(trifluoroacetyl)amino]ethoxy}benzoate (185 mg, 0.600 mmol), triethyl amine (0.190 mL, 1.32 mmol) and diphenylphosphoryl azide (0.130 mL, 0.66 mmol) in toluene was stirred at room temperature for 1 hour and at 93°C for 1.5 hours, and the reaction solution was cooled to room temperature. Methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (148 mg, 0.400 mmol) was added thereto and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water, extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 2:3), to obtain the titled compound as powder. 255 mg (94%)

^{1}H-NMR (DMSO-d6) δ; 3.50 to 3.54 (2H, m), 3.73 (3H, s), 3.89 (3H, s), 4.03 (2H, t, J = 5.2 Hz), 6.68 (1H, s), 6.81 to 7.61 (13H, m), 7.87 (1H, d, J = 2.4 Hz), 8.48 (1H, s), 8.53 (1H, s), 9.60 (1H, s)

(4) Methyl 5-[({[4-(2-aminoethoxy)-3-methoxyphenyl]amino}carbonyl)amino]-2-[bis(4-fluorophenyl)methoxy]benzoate

[0739] A suspension of methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3-methoxy-4-{2-[(trifluoroacetyl)amino]ethoxy} phenyl)amino]carbonyl}amino) benzoate (81.5 mg, 0.120 mmol), potassium carbonate (20 mg, 0.144 mmol) in methanol (2 mL) was stirred at room temperature for 15 hours and at 63°C for 4 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (chloroform:methanol = 3:1), to obtain the titled compound as powder. 49 mg (71%)

^{1}H-NMR (DMSO-d6) δ; 2.90 (2H, t, J = 5.6 Hz), 3.74 (3H, s), 3.88 (3H, s), 3.93 (2H, t, J = 5.6 Hz), 6.67 (1H, s), 6.82 to 7.60 (13H, m), 7.86 (1H, d, J = 2.4 Hz), 8.63 (1H, s), 8.70 (1H, s)

Example 451

Methyl 2-[(4-cyanophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0740] According to the same method as Example 236, the titled compound was synthesized.

(1) Methyl 2-[(4-cyanophenyl)(phenyl)methoxy]-5-nitrobenzoate

[0741] ^{1}H-NMR ($CDCl_3$) δ; 4.00 (3H, s), 6.45 (1H, s), 7.00 (2H, d, J = 9.2 Hz), 7.26 to 7.73 (9H, m), 8.22 (1H, dd, J = 3.2, 9.2 Hz), 8.75 (2H, d, J = 3.2 Hz)

(2) Methyl 2-[(4-cyanophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0742] ^{1}H-NMR (DMSO-d6) δ; 3.70 (3H, s), 3.72 (3H, s), 3.90 (3H, s), 6.77 (1H, s), 6.85 to 7.90 (15H, m), 8.45 (1H, s), 8.53 (1H, s)

Example 452

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(ethoxymethoxy)-3-methoxyphenyl]amino}carbonyl)amino]benzoate

(1) 4-(ethoxymethoxy)-3-methoxy benzoate

[0743] A solution (10 mL) of 4-hydroxy-3-methoxybenzaldehyde (1.53 g, 10.0 mmol), potassium carbonate (1.66 g, 12.0 mmol) and chloromethylethyl ether (1.12 mL, 12.0 mmol) in DMF was stirred at room temperature for 2 hours, the reaction solution was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. To the residue were added acetic acid (12 mL) and sulfamic acid (1.17 g, 12.0 mmol), and to this solution was added a solution of sodium chlorite (1.25 g, 11.0 mmol) in water (3 mL). The mixture was stirred at room temperature for 1 hour, water (50 mL) was added thereto, to obtain the titled compound as a solid. 1.64 g (63%)
^{1}H-NMR (DMSO-d6) δ; 1.13 (3H, t, J = 6.8 Hz), 3.67 (2H, q, J = 6.8 Hz), 3.82 (3H, s), 5.29 (2H, s), 7.15 (1H, d, J = 8.8 Hz), 7.48 (1H, d, J = 2.0 Hz), 7.53 (1H, dd, J = 2.0, 8.8 Hz)

(2) Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[4-(ethoxymethoxy)-3-methoxyphenyl]amino}carbonyl)amino]benzoate

[0744] A solution (10 mL) of 4-(ethoxymethoxy)-3-methoxy benzoate (227 mg, 1.00 mmol), triethyl amine (0.170 mL, 1.10 mmol) and diphenylphosphoryl azide (0.240 mL, 1.10 mmol) in toluene was stirred at room temperature for 15 minutes and at 93°C for 1.5 hours, and the reaction solution was cooled to room temperature. Methyl 5-amino-2-[bis (4-fluorophenyl)methoxy]benzoate (259 mg, 0.700 mmol) was added thereto, and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water, extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as powder. 357 mg (86%)
^{1}H-NMR (DMSO-d6) δ; 1.13 (3H, t, J = 7.2 Hz), 3.67 (2H, q, J = 7.2 Hz), 3.74 (3H, s), 3.89 (3H, s), 5.08 (2H, s), 6.68 (1H, s), 6.79 to 7.61 (13H, m), 7.88 (1H, d, J = 2.8 Hz), 8.51 (1H, s), 8.55 (1H, s)

Example 453

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(4-{[(2,2-dimethylpropanoyl)oxy]methoxy}-3-methoxyphenyl)amino] carbonyl}amino)benzoate

(1) (4-Formyl-2-methoxyphenoxy)methyl pivalic acid

[0745] A solution (15 mL) of 4-hydroxy-3-methoxybenzaldehyde (1.53 g, 10.0 mmol), potassium carbonate (1.80 g, 13.0 mmol) and chloromethyl pivalic acid (1.89 mL, 13.0 mmol) in DMF was stirred at room temperature for 15 hours, the reaction solution was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 7:1), to obtain the titled compound as oil. 1.75 g (65%)

^{1}H-NMR ($CDCl_3$) δ; 1.21 (9H, s), 3.75 (3H, s), 5.88 (2H, s), 7.17 to 7.46 (3H, m), 9.90 (1H, s)

(2) 4-{[(2,2-Dimethylpropanoyl)oxy]methoxy}-3-methoxy benzoate

[0746] To a solution of (4-formyl-2-methoxyphenoxy)methyl pivalic acid (1.75 g, 6.50 mmol) were added acetic acid (8 mL) and sulfamic acid (0.850 g, 8.77 mmol), and to this solution was added.a solution of sodium chlorite (0.765 g, 8.450 mmol) in water (2 mL). The mixture was stirred at room temperature for 1 hour and water (20 mL) was added thereto, to obtain the titled compound as a solid. 1.53 g (83%)

^{1}H-NMR (DMSO-d6) δ; 1.12 (9H, s), 3.85 (3H, s), 5.85 (2H, s), 7.17 to 7.57 (3H, m), 12.81 (1H, bs)

(3) Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(4-{[(2,2-dimethylpropanoyl)oxy]methoxy}-3-methoxyphenyl)amino] carbonyl}amino)benzoate

[0747] A solution (10 mL) of 4-{[(2,2-dimethylpropanoyl)oxy]methoxy}-3-methoxy benzoate (283 mg, 1.00 mmol), triethyl amine (0.308 mL, 2.20 mmol) and diphenylphosphoryl azide (0.240 mL, 1.10 mmol) in toluene was stirred at room temperature for 15 minutes and at 93°C for 1.5 hours, and the reaction solution was cooled to room temperature. Methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate (259 mg, 0.700 mmol) was added thereto, and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water, extracted with ethyl acetate, and the extracted solution was washed with water. The extracted solution was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as powder. 453 mg (100%)

^{1}H-NMR (DMSO-d6) δ; 1.12 (9H, s), 3.75 (3H, s), 3.89 (3H, s), 5.62 (2H, s), 6.68 (1H, s), 6.83 to 7.61 (13H, m), 7.88 (1H, d, J = 2.8 Hz), 8.57 (2H, s)

Example 454

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[3-methoxy-4-(methoxymethoxy)benzyl]amino}carbonyl)amino]benzoate

(1) Methyl [3-methoxy-4-(methoxymethoxy)phenyl]acetate

[0748] A solution (20 mL) of methyl (4-hydroxy-3-methoxyphenyl)acetate (1.11 g, 5.65 mmol), diisopropylethyl amine (1.19 mL, 6.78 mmol) and chloromethylm ethyl ether (0.515 mL, 6.78 mmol) in methylene chloride was stirred under ice-cooling for 1 hour and at room temperature for 3 hours, and the solvent was distilled off under reduced pressure. The residue was poured into water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 7:3), to obtain the titled compound as oil. 930 mg (68%)

^{1}H-NMR ($CDCl_3$) δ; 3.51 (3H, s), 3.57 (2H, s), 3.70 (3H, s), 3.88 (3H, s), 5.21 (2H, s), 6.78 to 7.11 (3H, m)

(2) [3-Methoxy-4-(methoxymethoxy)phenyl]acetic acid

[0749] To a solution of methyl [3-methoxy-4-(methoxymethoxy)phenyl]acetate (930 mg, 3.87 mmol) in methanol (5 mL) was added 1N aqueous solution of sodium hydroxide (4 mL), and the mixture was stirred at room temperature for 1 hour. The reaction solution was poured into water, washed with ether, neutralized with 1 N hydrochloric acid, and was extracted with ethyl acetate.

[0750] The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure, to obtain the titled compound as a solid. 875 mg (100%)

^{1}H-NMR ($CDCl_3$) δ; 3.51 (3H, s), 3.60 (2H, s), 3.87 (3H, s), 5.21 (2H, s), 6.79 to 7.12 (3H, m)

(3) Methyl 2-[bis(4-fluorophenyl)methoxy]-5-[({[3-methoxy-4-(methoxymethoxy)benzyl]amino}carbonyl)amino] benzoate

[0751] From [3-methoxy-4-(methoxymethoxy)phenyl]acetic acid and methyl 5-amino-2-[bis(4-fluorophenyl)methoxy] benzoate was synthesized the titled compound in the same manner as Example 453.

^{1}H-NMR (DMSO-d6) δ; 3.37 (3H, s), 3.75 (3H, s), 3.88 (3H, s), 4.20 (2H, d, J = 5.6 Hz), 5.09 (2H, s), 6.51 (1H, t, J = 5.6 Hz), 6.65 (1H, s), 6.80 to 7.60 (13H, m), 7.81 (1H, d, J = 2.8 Hz), 8.50 (1H, s)

Example 455

Methyl 2-[bis(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxybenzyl)amino]carbonyl}amino)benzoate

[0752] From (3,4-dimethoxyphenyl)acetic acid and methyl 5-amino-2-[bis(4-fluorophenyl)methoxy]benzoate was synthesized the titled compound in the same manner as Example 453.

^{1}H-NMR (DMSO-d6) δ; 3.72 (3H, s), 3.78 (3H, s), 4.19 (2H, d, J = 5.6 Hz), 6.48 (1H, t, J = 5.6 Hz), 6.65 (1H, s), 6.79 to 7.60 (13H, m), 7.82 (1H, d, J = 1.6 Hz), 8.49 (1H, s)

Example 456

Methyl 2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

(1) (4-Chlorophenyl)(2-fluorophenyl)methanol

[0753] To a solution of 2-fluorobromobenzene (9.2 g, 52.6 mmol) in THF (200 mL) was added dropwise 1.6N solution of butyl lithium in hexane (40 mL, 65 mmol) at -78°C, and the mixture was stirred at -78°C for 10 minutes. A solution (30 mL) of 4-chlorobenzaldehyde (8.9 g, 63.2 mmol) in THF was added dropwise thereto, and the mixture was stirred at - 78 to -65°C for 1 hour. The reaction solution was poured into an aqueous solution of saturated ammonium chloride, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 4:1), to obtain the titled compound as oil. 6.6 g (42.7%)

^{1}H-NMR ($CDCl_3$) δ: 2.31 (1H, d, J = 4.1 Hz), 6.12 (1H, d, J = 4.1 Hz), 7.02 (1H, ddd, J = 1.2, 8.3 and 10.5 Hz), 7.15 (1H, td, J = 1.2 and 7.5 Hz), 7.25 to 7.36 (5H, m), 7.47 (1H, td, J = 1.7 and 7.5 Hz)

(2) Methyl 2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-nitrobenzoate

[0754] A mixture of methyl 2-hydroxy-5-nitrobenzoate (2.1 g, 10.6 mmol), (4-chlorophenyl)(2-fluorophenyl)methanol (3.0 g, 12.7 mmol), 40% solution of diethyl azodicarbonate in toluene (7.4 g, 17.0 mmol) and a solution (10 mL) of triphenylphosphine (3.3 g, 12.7 mmol) in acetonitrile was stirred at room temperature for 12 hours, the reaction solution was poured into ice-water, and was extracted with ethyl acetate. The extracted solution was washed with water, was dried with anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 5:1), to obtain the titled compound as oil. 1.7 g (38.6%)

^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 6.77 (1H, m), 7.02 to 7.18 (4H, m), 7.26 to 7.36 (2H, m), 7.54 (2H, m, J = 8.6 Hz), 7.64 (1H, td, J = 1.7 and 7.7 Hz), 8.23 (1H, dd, J = 2.9 and 9.3 Hz), 8.75 (1H, d, J = 2.9 Hz)

IR (KBr) cm^{-1}: 1734, 1620, 1580, 1525, 1489, 1346, 1277

(3) Methyl 5-amino-2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]benzoate

[0755] A mixture of methyl 2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-nitrobenzoate (1.6 g, 3.9 mmol), iron (1.1 g, 19.2 mmol), calcium chloride (211 mg, 1.9 mmol), ethanol (25 mL) and water (5 mL) was stirred at reflux temperature for 2 hours. The insolubles were filtered off, and the filtrate was concentrated. The residue was dried under reduced pressure to obtain the titled compound as oil. 1.4 g (94.3%)

^{1}H-NMR ($CDCl_3$) δ: 3.47 (2H, br), 3.85 (3H, s), 6.49 (1H, s), 6.64 (1H, dd, J = 2.9 and 8.3 Hz), 6.70 (1H, d, J = 8.5 Hz), 6.98 to 7.36 (6H, m), 7.49 (2H, d, J = 7.8 Hz), 7.69 (1H, td, J = 1.7 and 7.5 Hz)

IR (KBr) cm^{-1}: 1721, 1491, 1448, 1250, 1220, 100, 788

(4) Methyl 2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0756] To a solution (20 mL) of methyl 5-amino-2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]benzoate (1.35 g, 3.5 mmol) in THF was added 3,4-dimethoxyphenyl isocyanate (0.75 g, 4.2 mmol) under ice-cooling, the mixture was stirred at 0°C for 1 hour and at room temperature for 12 hours, and the solvent was distilled off under reduced pressure. The residue was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 1.36 g (65.7%)

^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 6.46 (1H, s), 6.58 (2H, m), 6.73 (1H, dd, J = 8.5 and 2.4 Hz), 6.79 to 6.86 (2H, m), 6.97 to 7.30 (6H, m), 7.46 (1H, dd, J = 8.5 and 2.4 Hz), 7.49 (1H, m), 7.51 (1H,m), 7.63 to 7.68 (2H, m)

IR (KBr) cm^{-1}: 1725, 1650, 1590, 1556, 149, 1448, 1222, 1082, 1014, 786
LC/MS (APCI+) m/z: 587.1 (Na^+)

Example 457

N-(tert-butyl)-2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide

(1) 2-[(4-Chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0757] To a solution (25 mL) of methyl 2-{(4-chlorophenyl)(2-fluorophenyl)methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate (0.8 g, 1.42 mmol) in methanol was added 1N aqueous solution of sodium hydroxide (4 mL) at reflux temperature, and the mixture was stirred for 3 hours. The reaction solution was poured into water, and neutralized with 1N-hydrochloric acid. The precipitated crystals were collected, washed with water, and dried under reduced pressure to obtain the titled compound as a solid. 790 mg (100%)

^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 3.87 (3H, s), 6.71 (1H, s), 6.83 (1H, d, J = 8.5 Hz), 6.89(1H, dd, J = 2.4 and 8.5 Hz), 6.94 (1H, d, J = 9.3 Hz), 7.11 to 7.43 (11H, m), 7.73 (1H, d, J = 2.9 Hz), 8.21 (1H, dd, J = 2.8 and 9.3 Hz), 11.0 (1H, br)
IR (KBr) cm^{-1}: 3330, 2919, 1700, 1610, 1520, 1493, 1222, 761

(2) N-(tert-Butyl)-2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide

[0758] A mixed solution of 2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl} amino)benzoate (600 mg, 1.09 mmol), 1-hydroxy-1H-benzotriazole (250 mg, 1.64 mmol), tert-butyl amine (160 mg, 2.18 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (261 mg, 1.36 mmol) and DMF (6 mL) was stirred under ice-cooling for 1 hour and at room temperature for 12 hours, was poured into water, and the precipitates were collected. This was purified by silicagel column chromatography (hexane:ethyl acetate = 1:1), to obtain the titled compound as a solid. 620 mg (93.9%)

^{1}H-NMR ($CDCl_3$) δ: 1.22 (9H, s), 3.82 (3H, s), 3.83 (3H, s), 6.52 (1H, s), 6.71 to 6.77 (3H, m), 7.06 to 7.15 (3H, m), 7.27 to 7.36 (7H, m), 7.53 (1H, s), 7.64 to 7.67 (2H, m), 7.71 (1H, dd, J = 2.8 and 8.9 Hz)
IR (KBr) cm^{-1}: 3360, 1663, 1610, 1546, 1515, 1491, 1206, 1093, 1028, 910, 812, 761, 733
LC/MS (APCI +) m/z: 628.1 (Na^+), 606.1 (M^+)

Example 458

Methyl 2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0759] The titled compound was synthesized in the same manner as Example 456.

(1) (4-Chlorophenyl)(3-fluorophenyl)methanol

[0760] ^{1}H-NMR ($CDCl_3$) δ: 2.31 (1H, d, J = 4.1 Hz), 5.80 (1H, d, J = 3.5 Hz), 6.93 to 6.99(1H, m), 7.07 to 7.13 (2H, m), 7.27 to 7.34 (5H, m)

(2) Methyl 2-{(4-chlorophenyl)(3-fluorophenyl)methoxy}-5-nitrobenzoate

[0761] ^{1}H-NMR ($CDCl_3$) δ: 4.00 (3H, s), 6.37 (1H, s), 6.96 to 7.13 (3H, m), 7.25 to 7.36 (4H, m), 7.45 to 7.48 (2H, m), 8.21 (1H, dd, J = 2.9 and 9.3 Hz), 8.75 (1H, d, J = 2.9 Hz)
IR (KBr) cm^{-1}: 3464, 1734, 1614, 1591, 1522, 1489, 1442, 1346, 1279, 1130, 1076, 1014, 824, 788, 771

(3) Methyl 5-amino-2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]benzoate

[0762] ^{1}H-NMR ($CDCl_3$) δ: 3.49(2H, brs), 3.85 (3H, s), 6.07 (1H, m), 6.25 (2H, d, J = 1.7 Hz), 6.9 to 7.5 (9H, m)
IR (KBr) cm^{-1}: 3367, 1723, 1591, 1492, 1222, 1014, 786

(4) Methyl 2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0763] ^{1}H-NMR ($CDCl_3$) δ: 3.79(3H, s), 3.80 (3H, s), 3.85 (3H, s), 6.12 (1H, s), 6.66 (1H, dd, J = 2.4 and 8.5 Hz),

6.71 to 6.75 (2H, m), 6.88 (1H, s), 6.90 to 7.00 (3H, m), 7.17 to 7.29(5H, m), 7.37 to 7.43 (3H, m), 7.61 (1H, d, J = 2.7 Hz)
IR (KBr) cm^{-1}: 3341, 1725, 1654, 1612, 1557, 1497, 1451, 1413, 1221, 1166, 1136, 1084, 1027, 910, 788, 772, 733
LC/MS (APCI +) m/z: 587.0 (Na^+), 565.0 (M^+)

Example 459

N-(tert-Butyl)-2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide

[0764] The titled compound was synthesized in the same manner as Example 457.

(1) 2-[(4-Chlorophenyl)(3-fluorophenyl)methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0765] ^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 3.86 (3H, s), 6.37 (1H, m), 6.82 (1H, d, J = 8.6 Hz), 6.88 to 6.92 (2H, m), 7.05 to 7.08 (2H, m), 7.15 (2H, m), 7.30 (2H, d, J = 8.3 Hz), 7.36 to 7.43 (4H, m), 7.58 (1H, brs), 7.71 (1H, d, J = 2.7 Hz), 8.23 (1H, dd, J = 2.7 and 9.1 Hz), 10.8 (1H, br)
IR (KBr) cm^{-1}: 3380, 1702, 1552, 1516, 1493, 1260, 1220, 1196

(2) N-(tert-Butyl)-2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide

[0766] ^{1}H-NMR ($CDCl_3$) δ: 1.21 (9H, s), 3.80 (3H, s), 3.82 (3H, s), 6.19(1H, s), 6.70 to 6.76 (3H, m), 7.00 to 7.05 (2H, m), 7.07 to 7.12 (2H, m), 7.23 to 7.26 (2H, m), 7.30 to 7.36 (3H, m), 7.43 (1H, s), 7.65 to 7.72 (4H, m)
IR (KBr) cm^{-1}: 3368, 1637, 1610, 1514, 1491, 1412, 1205, 1027, 733
LC/MS (APCI +) m/z: 628.1 (Na^+), 606.1 (M^+)

Example 460

Methyl 2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0767] The titled compound was synthesized in the same manner as Example 456.

(1) (4-Chlorophenyl)(4-fluorophenyl)methanol

[0768] ^{1}H-NMR ($CDCl_3$) δ: 2.24 (1H, d, J = 3.3 Hz), 5.80 (1H, d, J = 3.3 Hz), 6.99 to 7.05 (2H, m), 7.26 to 7.35 (6H, m)
IR (KBr) cm^{-1}: 3340, 1605, 1508, 1225, 1090, 1013, 830, 551

(2) Methyl 2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]-5-nitrobenzoate

[0769] ^{1}H-NMR ($CDCl_3$) δ: 3.98 (3H, s), 6.38 (1H, s), 6.96 to 7.08 (3H, m), 7.30 to 7.36 (3H, m), 7.43 to 7.50 (3H, m), 8.20 (1H, dd, J = 2.7 and 9.2 Hz), 8.73 (1H, d, J = 2.7 Hz)
IR (KBr) cm^{-1}: 1734, 1612, 1588, 1510, 1489, 1346, 1346, 1278, 1130, 1076, 1013, 822

(3) Methyl 5-amino-2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]benzoate

[0770] ^{1}H-NMR ($CDCl_3$) δ: 3.49(2H, br), 3.83 (3H, s), 6.07 (1H, s), 6.99(2H, d, J = 4.4 Hz), 6.98 to 7.05 (3H, m), 7.12 (1H, t, J = 1.6 Hz), 7.27 to 7.43 (5H, m)
IR (KBr) cm^{-1}: 1721, 1605, 1499, 1448, 1319, 1222, 1158, 1089, 1014, 816, 551

(4) Methyl 2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

[0771] ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 6.16 (1H, s), 6.59(1H, s), 6.70 to 6.80 (4H, m), 6.98 to 7.02 (3H, m), 7.27 to 7.31 (2H, m), 7.37 to 7.46 (5H, m), 7.62 (1H, d, J = 3.0 Hz)
IR (KBr) cm^{-1}: 3346, 1729, 1606, 1554, 1499, 1413, 1221, 1082, 1013, 815
LC/MS (APCI +) m/z: 587.0 (Na^+)

Example 461

N-(tert-Butyl)-2-[(4-chlorophenyl)(4-fluorophenyl)methoxy)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide

[0772] The titled compound was synthesized in the same manner as Example 457.

(1) 2-[(4-Chlorophenyl)(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate

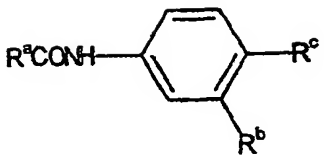
[0773] ^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 3.87 (3H, s), 6.40 (1H, s), 6.79 to 6.92 (4H, m), 7.03 to 7.12 (3H, m), 7.21 to 7.39(7H, m), 7.70 (1H, d, J = 2.9 Hz), 8.19(1H, d, J = 8.3 Hz), 10.2 (1H, br)
IR (KBr) cm^{-1}: 3381, 1699, 1607, 1542, 1509, 1491, 1222, 1026, 820

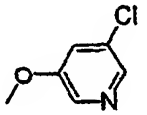
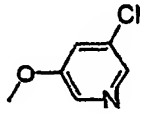
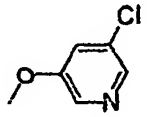
(2) N-(tert-Butyl)-2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino) benzamide

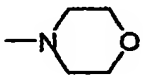
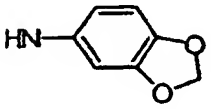
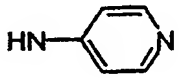
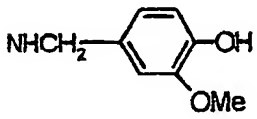
[0774] ^{1}H-NMR ($CDCl_3$) δ: 1.19 (9H, s), 3.82 (3H, s), 3.84 (3H, s), 6.22 (1H, s), 6.71 to 6.78 (3H, m), 7.03 to 7.09 (3H, m), 7.19 (1H, s), 7.23 to 7.29 (5H, m), 7.32 to 7.36 (1H, m), 7.46 (1H, s), 7.67 (1H, d, J = 2.7 Hz), 7.70 to 7.75 (2H, m)
IR (KBr) cm^{-1}: 3373, 1636, 1607, 1528, 1512, 1491, 1222, 1091, 1028, 816, 733

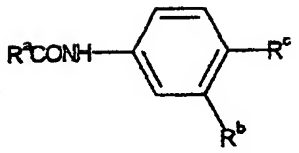
[0775] The structures of the compounds of Examples 1 to 461 are shown in the following Table 1.

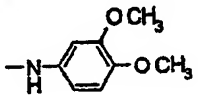
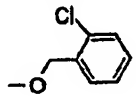
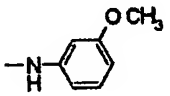
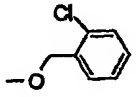
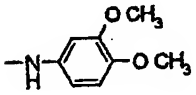
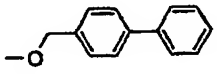
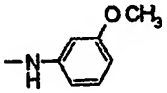
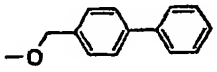
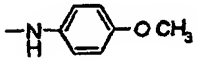
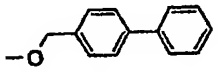
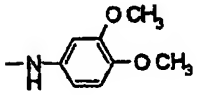
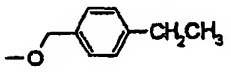
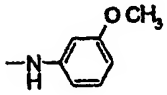
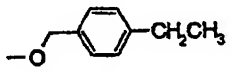
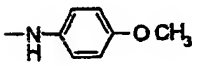
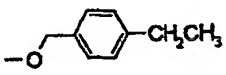
Table 1

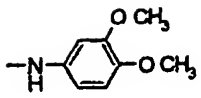
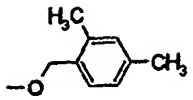
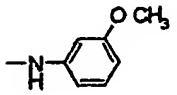
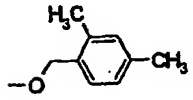
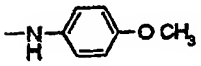
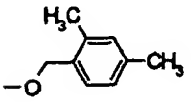
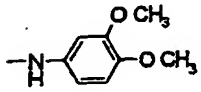
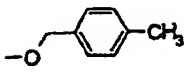
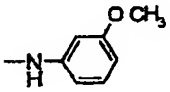
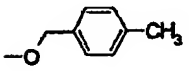
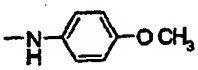
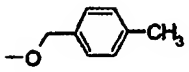
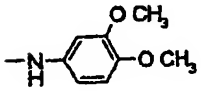
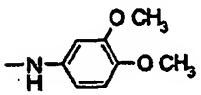
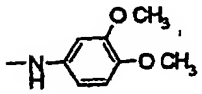
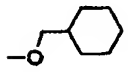
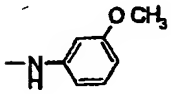
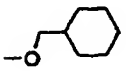
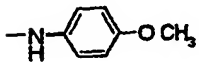
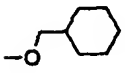


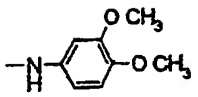
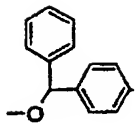
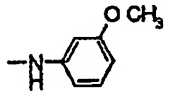
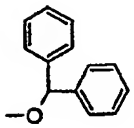
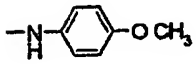
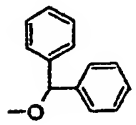
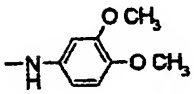
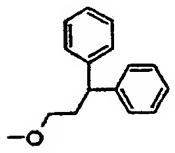
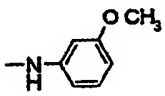
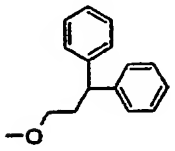
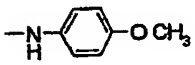
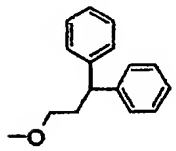
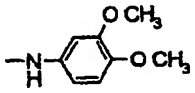
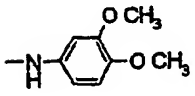
Example No.	R^a	R^b	R^c
1	NHPh	$COCH_2CH_3$	$OCHPh_2$
2	NHC_6H_3-3,4-$(OCH_3)_2$	$COCH_2CH_3$	$OCHPh_2$
3	NHC_6H_4-3-OCH_3	$COCH_2CH_3$	$OCHPh_2$
4	NHC_6H_4-4-OCH_3	$COCH_2CH_3$	$OCHPh_2$
5	NHC_6H_4-4-OCH_3	$COCH_2CH_2CH_3$	$OCHPh_2$
6	NHC_6H_4-3-OCH_3	$COCH_2CH_2CH_3$	$OCHPh_2$
7	NHC_6H_3-3,4-$(OCH_3)_2$	$COCH_2CH_2CH_3$	$OCHPh_2$
8	NHC_6H_4-4-OCH_3	$COCH_3$	$OCHPh_2$
9	NHC_6H_4-3-OCH_3	$COCH_3$	$OCHPh_2$
10	NHC_6H_3-3,4-$(OCH_3)_2$	$COCH_3$	$OCHPh_2$
11	NHC_6H_3-3,4-$(OCH_3)_2$	$COCH_2CH_3$	$OCH_2C_6H_4$-4-$C(CH_3)_3$
12	NHC_6H_4-4-OCH_3	$COCH_2CH_3$	$OCH_2C_6H_4$-4-$C(CH_3)_3$
13	NHC_6H_4-3-OCH_3	$COCH_2CH_3$	$OCH_2C_6H_4$-4-$C(CH_3)_3$
14	NHC_6H_3-3,4-$(OCH_3)_2$	$COCH_2CH_3$	$OCH_2C_6H_4$-4-$CH(CH_3)_2$
15	NHC_6H_4-4-OCH_3	$COCH_2CH_3$	$OCH_2C_6H_4$-4-$CH(CH_3)_2$
16	NHC_6H_4-3-OCH_3	$COCH_2CH_3$	$OCH_2C_6H_4$-4-$CH(CH_3)_2$
17	NHC_6H_3-3,4-$(OCH_3)_2$	$COCH_2CH_3$	
18	NHC_6H_4-4-OCH_3	$COCH_2CH_3$	
19	NHC_6H_4-3-OCH_3	$COCH_2CH_3$	
20	NHC_6H_4-4-OCH_3	$CONHC(CH_3)_3$	$OCHPh_2$
21	NHC_6H_3-3,4-$(OCH_3)_2$	$CONHC(CH_3)_3$	$OCHPh_2$
22	NHPh	$COOCH_3$	$OCHPh_2$
23	NHC_6H_4-4-OCH_3	$COOCH_3$	$OCHPh_2$

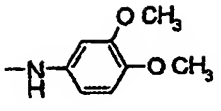
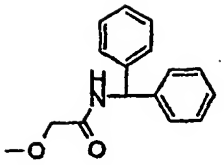
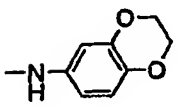
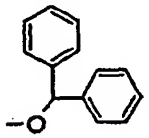
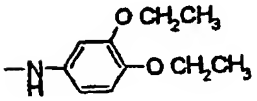
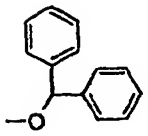
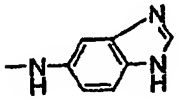
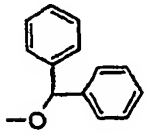
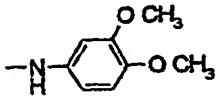
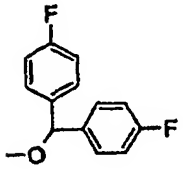
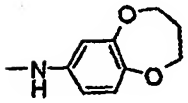
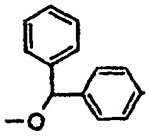
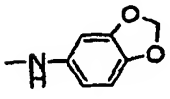
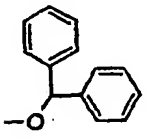
24	NHC_6H_4-3-OCH_3	$COOCH_3$	$OCHPh_2$
25	NHC_6H_4-4-OCH_2CH_3	$COOCH_3$	$OCHPh_2$
26	NHC_6H_3-3,4-$(OCH_3)_2$	$COOCH_3$	$OCHPh_2$
27	NHC_6H_4-3-OCH_2CH_3	$COOCH_3$	$OCHPh_2$
28	NHC_6H_4-3-NO_2	$COOCH_3$	$OCHPh_2$
29		$COOCH_3$	$OCHPh_2$
30		$COOCH_3$	$OCHPh_2$
31	NHC_6H_4-3-$COCH_3$	$COOCH_3$	$OCHPh_2$
32		$COOCH_3$	$OCHPh_2$
33	NHPh	$CONHC(CH_3)_3$	$OCHPh_2$
34	NHPh	$CONHC(CH_3)_2CH_2CH_3$	$OCHPh_2$
35	NHPh	$CONHC(CH_3)_2Ph$	$OCHPh_2$
36	NHC_6H_4-4-OCH_3	$COOC(CH_3)_3$	$OCHPh_2$
37	NHC_6H_4-4-OCH_3	$COOCH(CH_3)_2$	$OCHPh_2$
38		$COOCH_3$	$OCHPh_2$

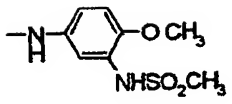
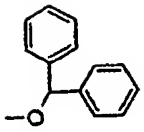
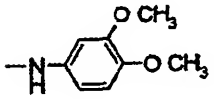
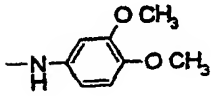
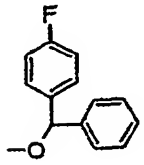
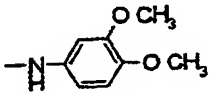
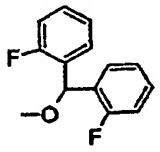
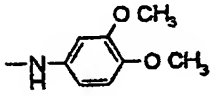
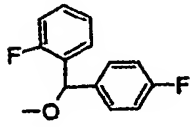
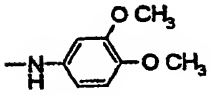
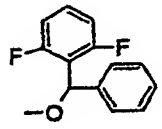
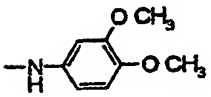
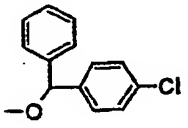
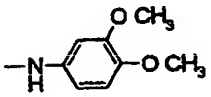
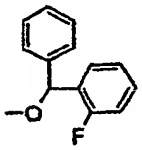


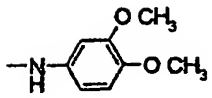
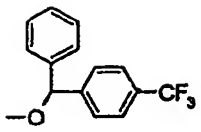
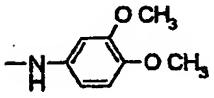
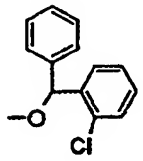
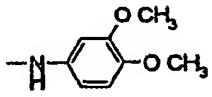
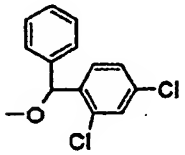
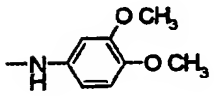
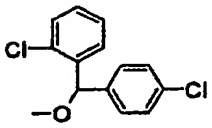
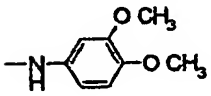
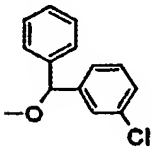
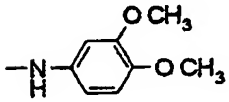
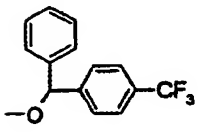
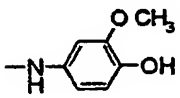
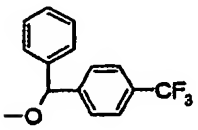
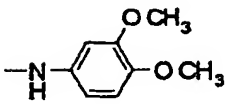
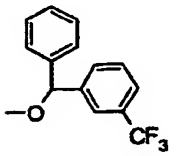
Example No.	R^a	R^b	R^c
39		$COCH_2CH_3$	
40		$COCH_2CH_3$	
41		$COCH_2CH_3$	
42		$COCH_2CH3$	
43		$COCH_2CH_3$	
44		$COCH_2CH_3$	
45		$COCH_2CH_3$	
46		$COCH_2CH_3$	

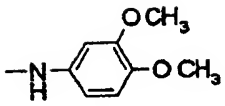
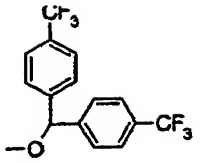
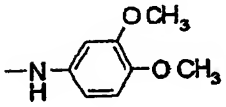
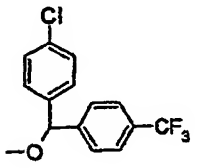
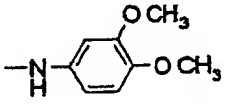
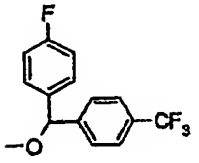
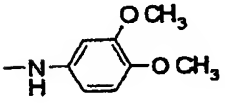
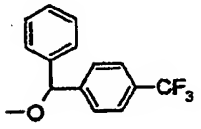
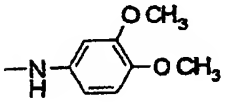
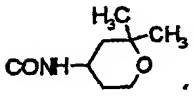
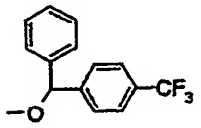
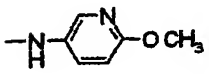
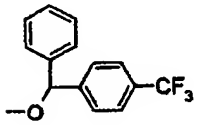
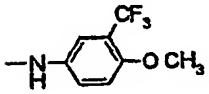
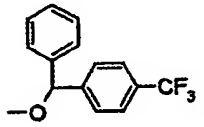
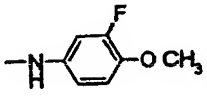
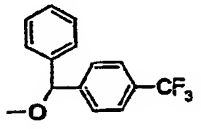
47		$COCH_2CH_3$	
48		$COCH_2CH_3$	
49		$COCH_2CH_3$	
50		$COCH_2CH_3$	
51		$COCH_2CH_3$	
52		$COCH_2CH_3$	
53		$COCH_2CH_3$	$OCH_2C(CH_3)_3$
54		$COCH_2CH_3$	$OCH_2CH(CH_3)_2$
55		$COCH_2CH_3$	
56		$COCH_2CH_3$	
57		$COCH_2CH_3$	

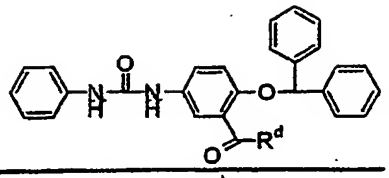
58		$COCH(CH_3)_2$	
59		$COCH(CH_3)_2$	
60		COCH(CH3)2	
61		$COCH_2CH_3$	
62		$COCH_2CH_3$	
63		$COCH_2CH_3$	
64		$COCH_2CH_3$	OCH_2COOCH_3
65		$COCH_2CH_3$	OCH_2COOH

66		$COCH_2CH_3$	
67		$COCH(CH_3)_2$	
68		$COCH(CH_3)_2$	
69		$COCH(CH_3)_2$	
70		$COCH(CH_3)_2$	
71		$COCH(CH_3)_2$	
72		$COCH(CH_3)_2$	

73		$COCH(CH_3)_2$	
74		$COOCH_3$	
75		$COOCH_3$	
76		$COOCH_3$	
77		$COOCH_3$	
78		$COOCH_3$	
79		$COOCH_3$	
80		$COOCH_3$	

81		$COOCH_3$	
82		$COOCH_3$	
83		$COOCH_3$	
84		$COOCH_3$	
85		$COOCH_3$	
86		$CONHC(CH_3)_3$	
87		$COOCH_3$	
88		$COOCH_3$	

89		$COOCH_3$	
90		$COOCH_3$	
91		$COOCH_3$	
92		$CONHCH(CH_3)_2$	
93			
94		$COOCH_3$	
95		$COOCH_3$	
96		$COOCH_3$	



Example No.	R^d
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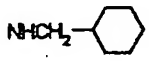
98	
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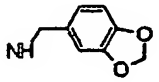
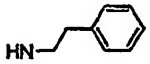
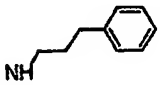
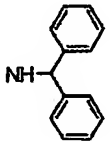
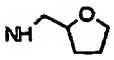
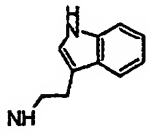
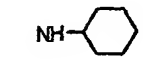
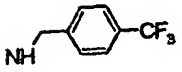
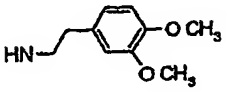
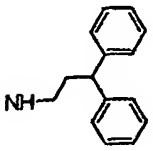
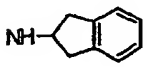
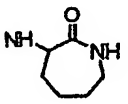
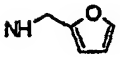
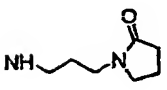
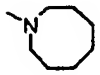
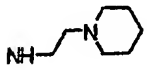
100	
101	
102	
103	
104	$NH(CH_2)_2OCH_3$
105	$NH(CH_2)_3SCH_3$
106	
107	

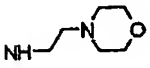
108	$NHCH(CH_2CH_3)_2$
109	
110	$NHCH_2CCH$
111	
112	
113	
114	
115	$NH(CH_2)_3OCH(CH_3)_2$
116	
117	
118	

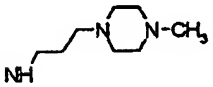
119 

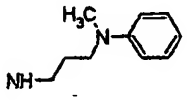
120 $NH(CH_2)_2N(CH_3)_2$

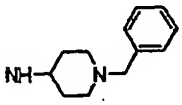
121 $NH(CH_2)_3N(CH_2CH_3)_2$

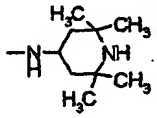
122 

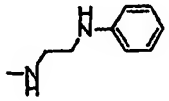
123 

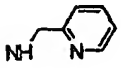
124 

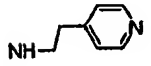
125 

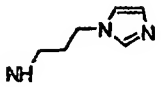
126 

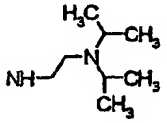
127 

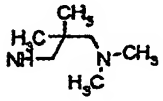
128 

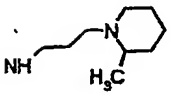
129 

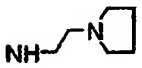
130 

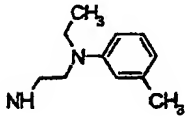
131 

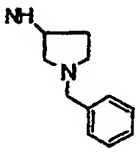
132 

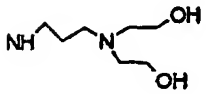
133 

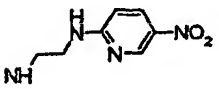
134 

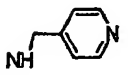
135 

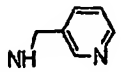
136 

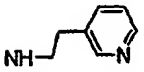
137 

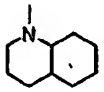
138 

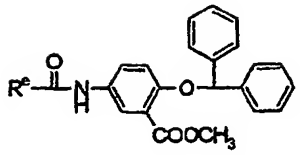
139 

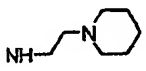
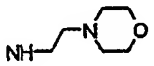
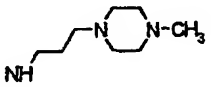
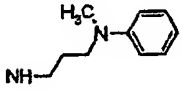
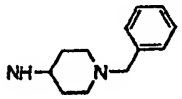
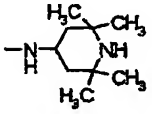
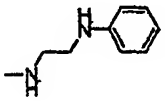
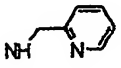
140 

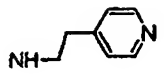
141 

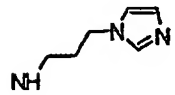
142 

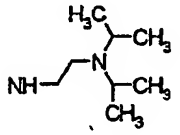
143 

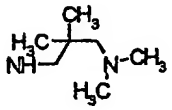


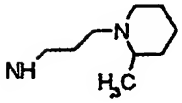
Example No.	R^e
144	$NH(CH_2)_2N(CH_3)_2$
145	$NH(CH_2)_3N(CH_2CH_3)_2$
146	
147	
148	
149	
150	
151	
152	
153	

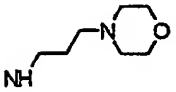
154 

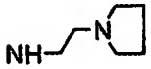
155 

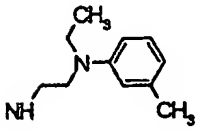
156 

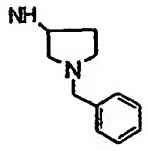
157 

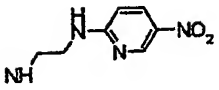
158 

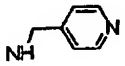
159 

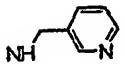
160 

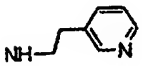
161 

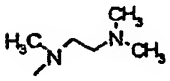
162 

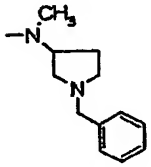
163 

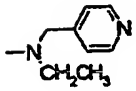
164 

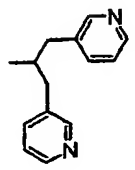
165 

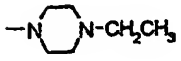
166 

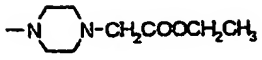
167 

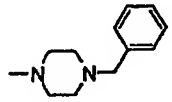
168 

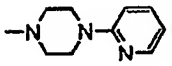
169 

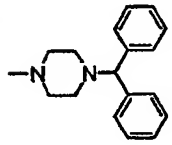
170 

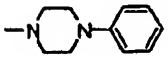
171 

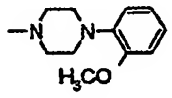
172 

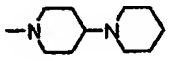
173 

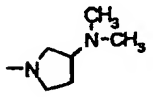
174 

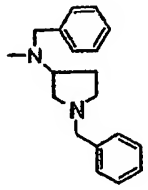
175 

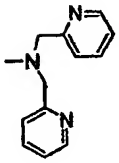
176 

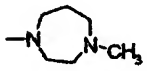
177 

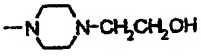
178 

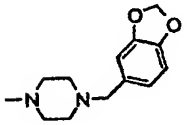
179 

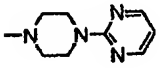
180 

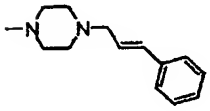
181 

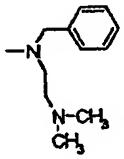
182 

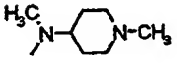
183 

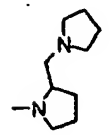
184 

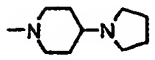
185 

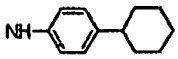
186 

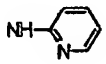
187 

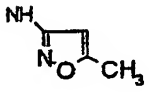
188 

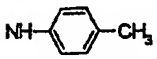
189 

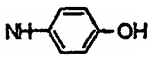
190 

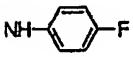
191 

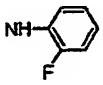
192 

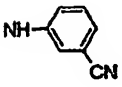
193 

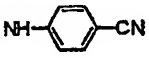
194 

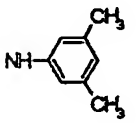
195 

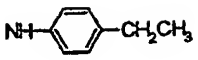
196 

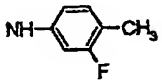
197 

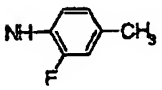
198 

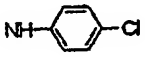
199 

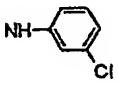
200 

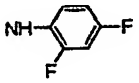
201 

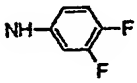
202 

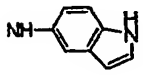
203 

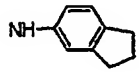
204 

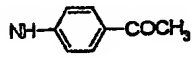
205 

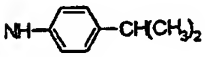
206 

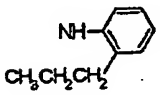
207 

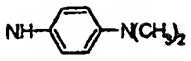
208 

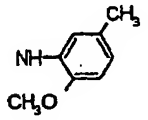
209 

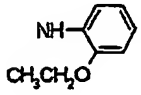
210 

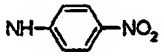
211 

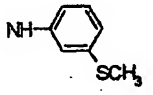
212 

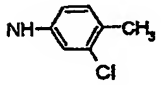
213 

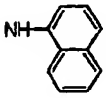
214 

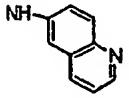
215 

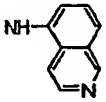
216 

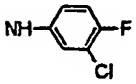
217 

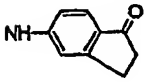
218 

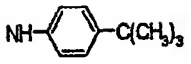
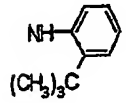
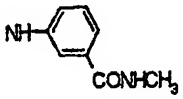
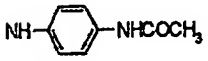
219 

220 

221 

222 

223 

224		
225		
226		
227		

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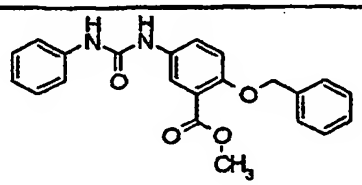
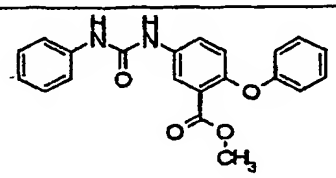
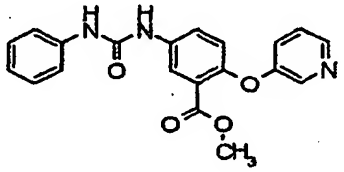
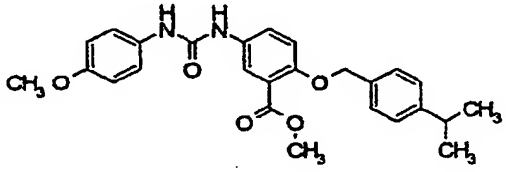
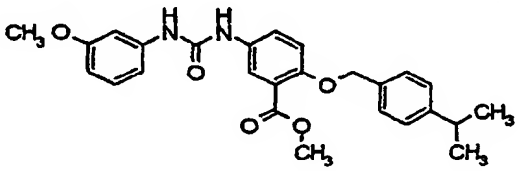
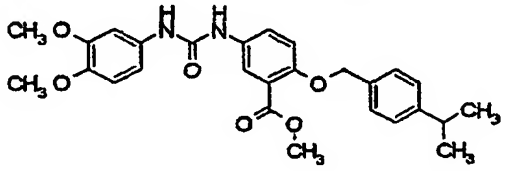
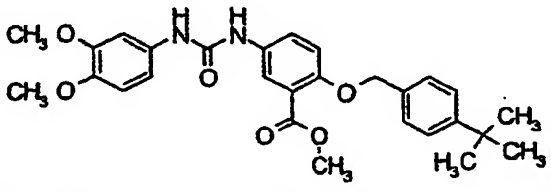
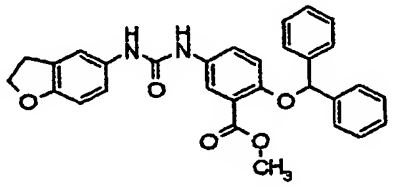
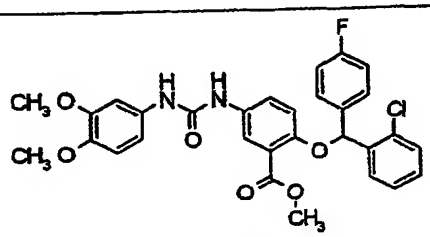
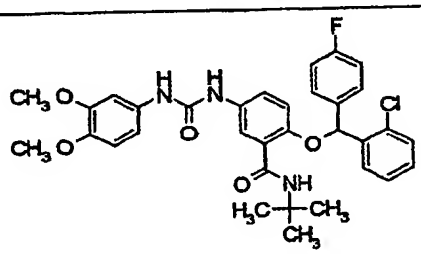
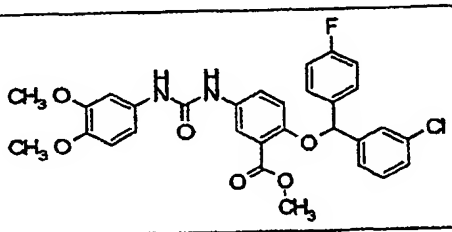
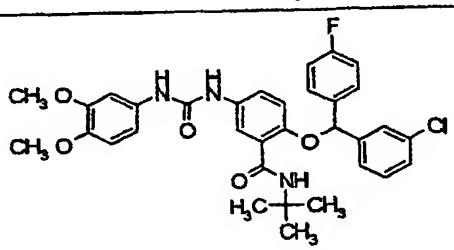
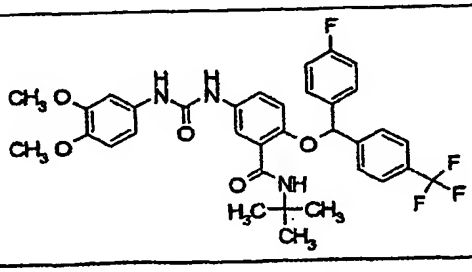
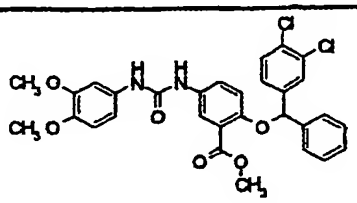
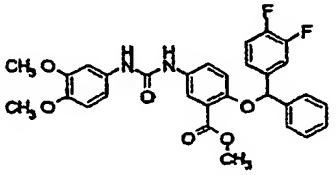
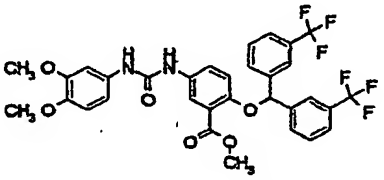
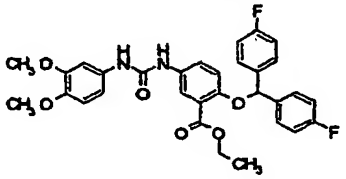
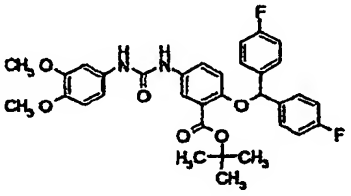
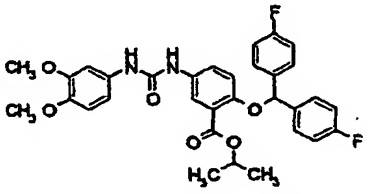
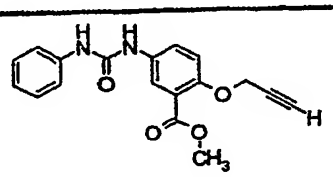
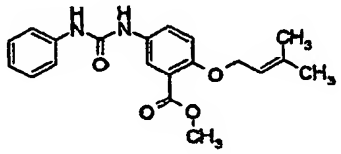
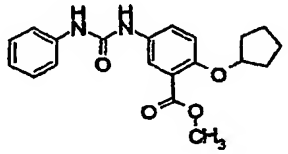
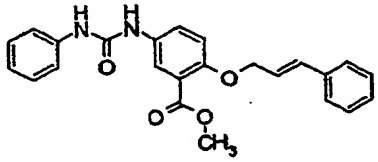
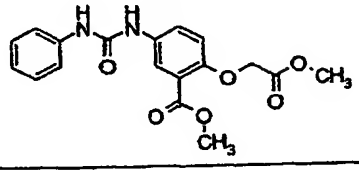
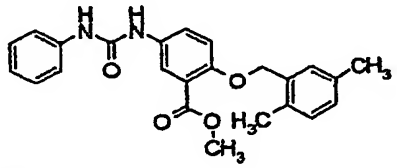
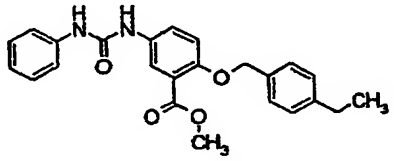
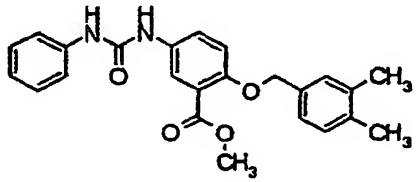
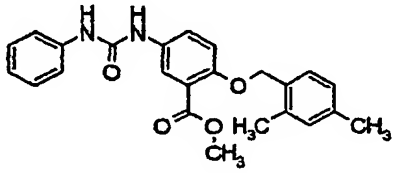
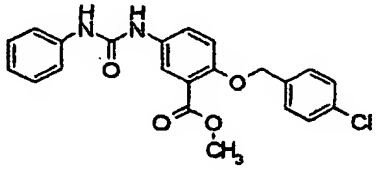
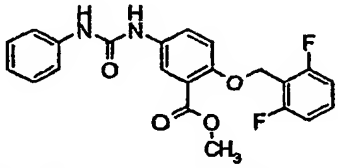
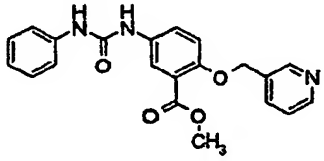
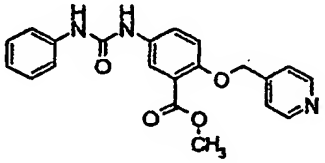
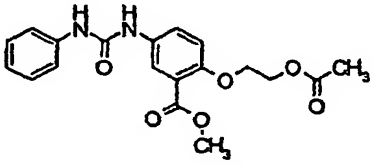
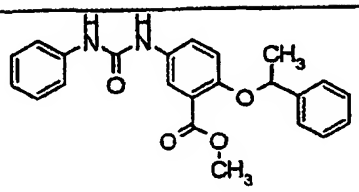
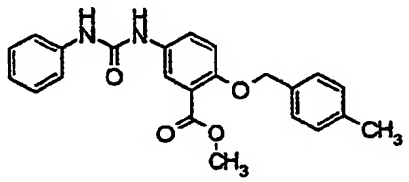
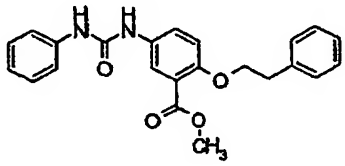
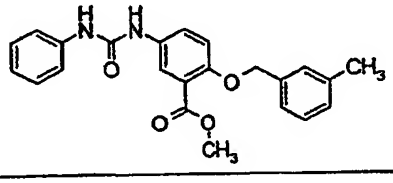
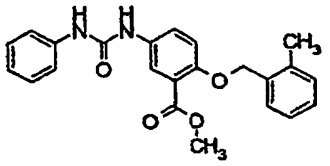
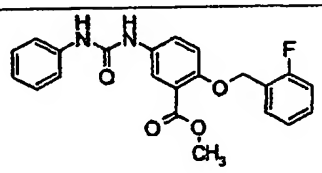
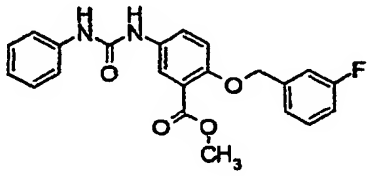
228	
229	
230	
231	
232	
233	
234	

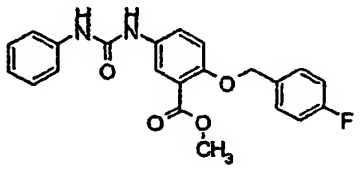
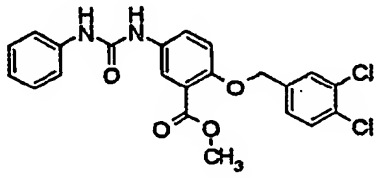
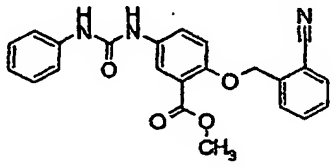
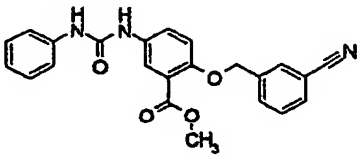
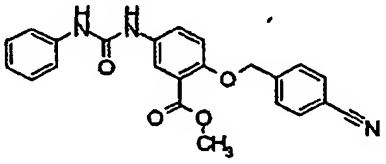
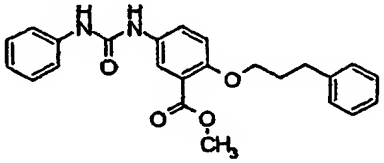
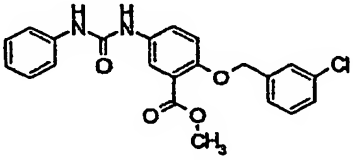
235	
236	
237	
238	
239	
240	

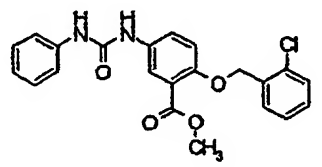
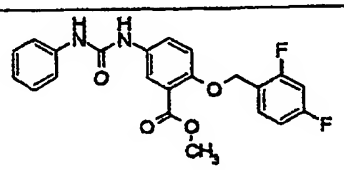
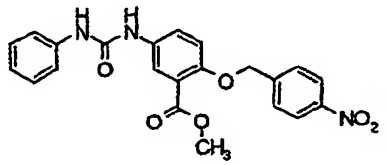
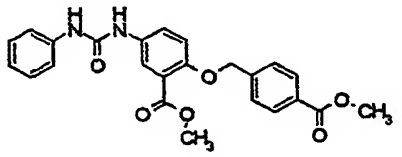
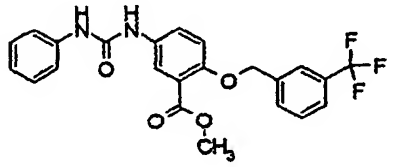
Example No.	Structure Formula
241	
242	
243	
244	
245	
246	

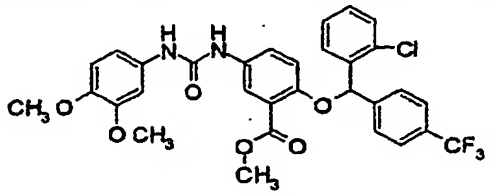
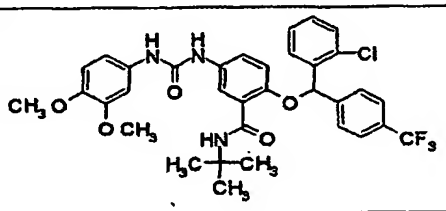
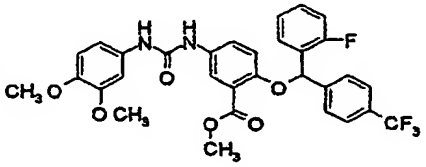
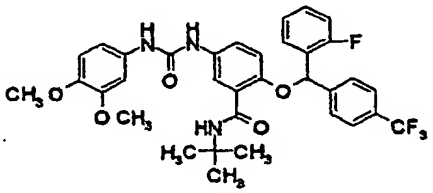
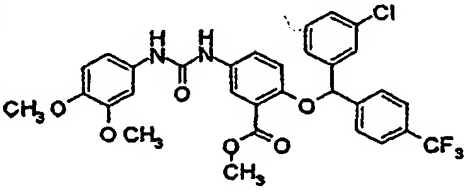
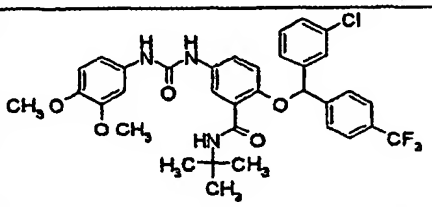
Example No.	Structure Formula
247	
248	
249	
250	
251	
252	
253	

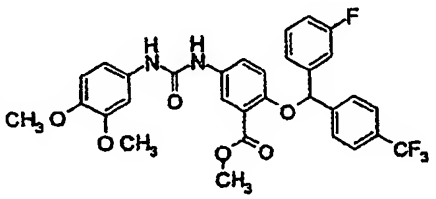
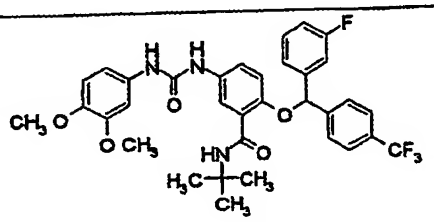
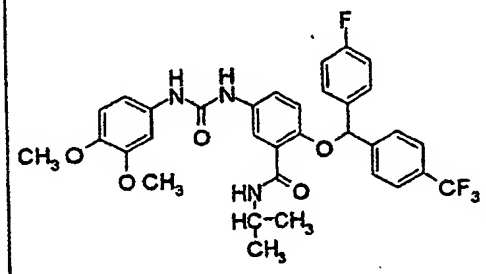
254	
255	
256	
257	
258	
259	
260	

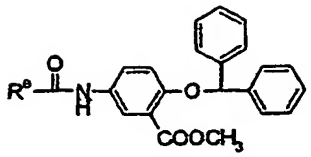
261	
262	
263	
264	
265	
266	
267	

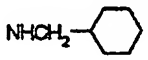
268	
269	
270	
271	
272	
273	
274	

275	
276	
277	
278	
279	

Example No.	Structure Formula
280	
281	
282	
283	
284	
285	

286	
287	
288	



Example No.	R^e
289	$NH(CH_2)_3CH_3$
290	
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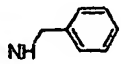
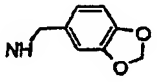
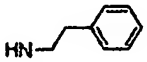
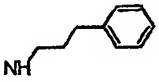
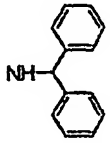
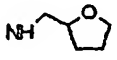
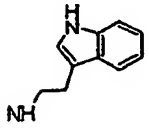
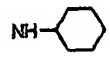
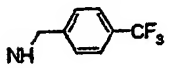
292	
293	
294	
295	
296	
297	$NH(CH_2)_2OCH_3$
298	$NH(CH_2)_3SCH_3$
299	
300	

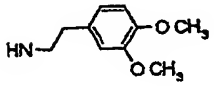
301 $NHCH(CH_2CH_3)_2$

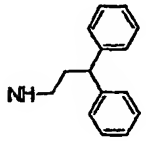
302 $NHC(CH_3)_3$

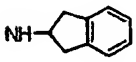
303 

304 $NHCH_2CCH$

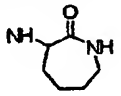
305 

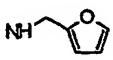
306 

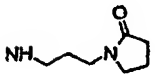
307 

308 

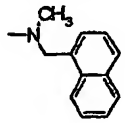
309 $NH(CH_2)_3OCH(CH_3)_2$

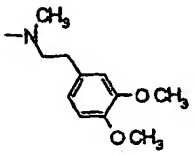
310 

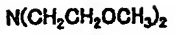
311 

312 

313 $N(CH_2CH_2CH_3)_2$

314 

315 

316 

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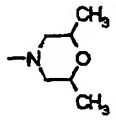
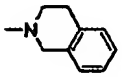
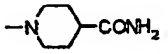
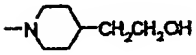
318 

319 

320 

321 

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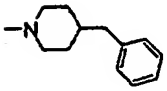
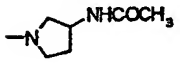
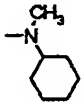
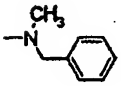
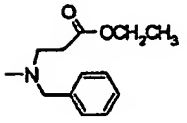
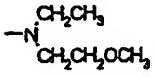
323 

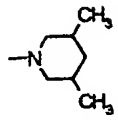
324 

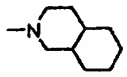
325 

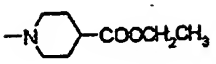
326 

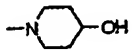
327 

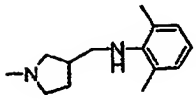
328 

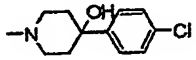
329 

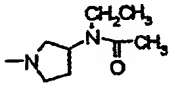
330 

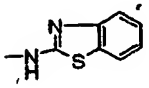
331 

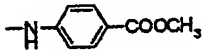
332 

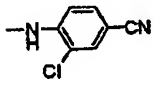
333 

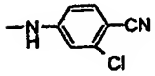
334 

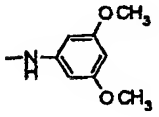
335 

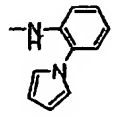
336 

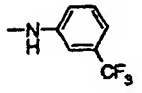
337 

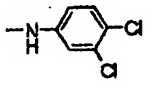
338 

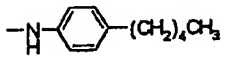
339 

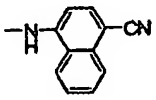
340 

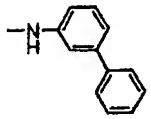
341 

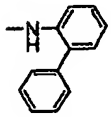
342 

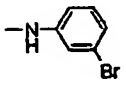
343 

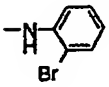
344 

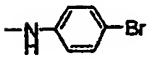
345 

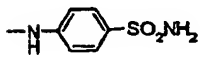
346 

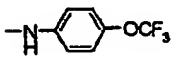
347 

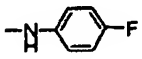
348 

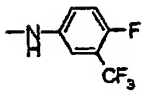
349 

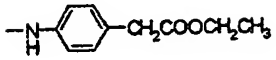
350 

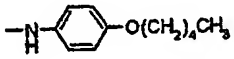
351 

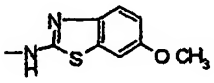
352 

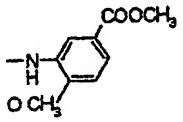


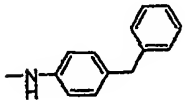
353 

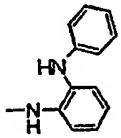
354 

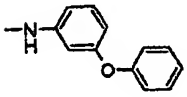
355 

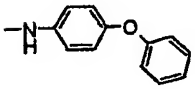
356 

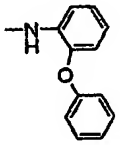
357 

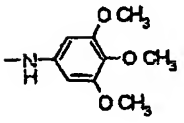
358 

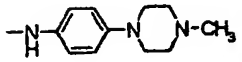
359 

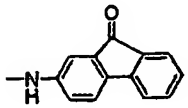
360 

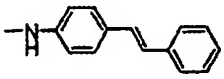
361 

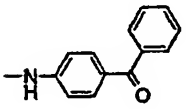
362 

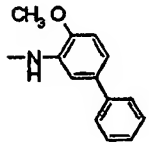
363 

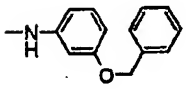
364 

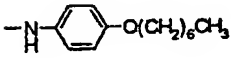
365 

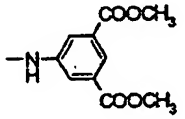
366 

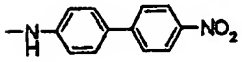
367 

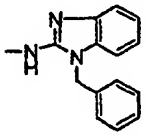
368 

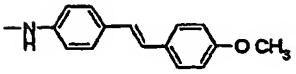
369 

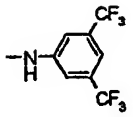
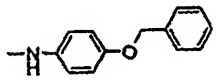
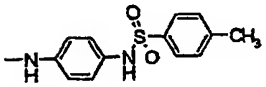
370 

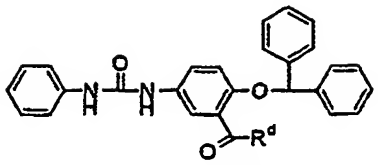
371 

372 

373 

374 

375	
376	
377	



Example No.	R^d
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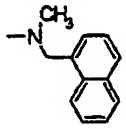
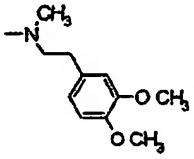
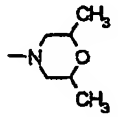
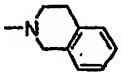
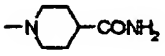
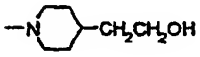
379	
380	
381	$N(CH_2CH_2OCH_3)_2$
382	
383	
384	
385	
386	
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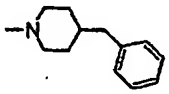
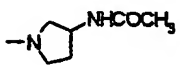
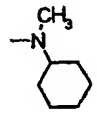
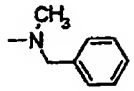
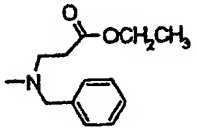
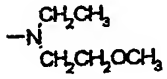
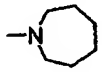
388	
389	

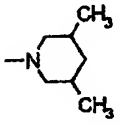
390 

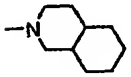
391 

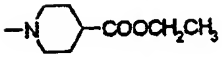
392 

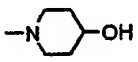
393 

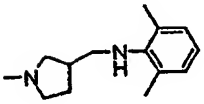
394 

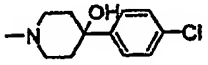
395 

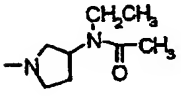
396 

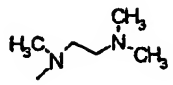
397 

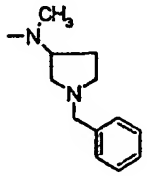
398 

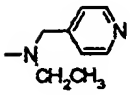
399 

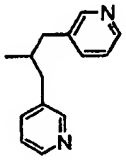
400 

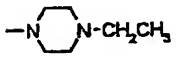
401 

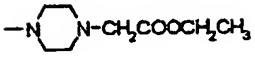
402 

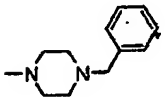
403 

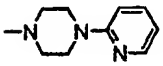
404 

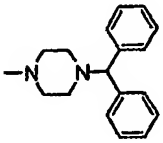
405 

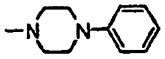
406 

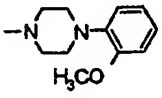
407 

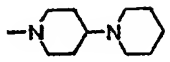
408 

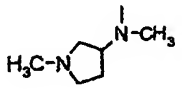
409 

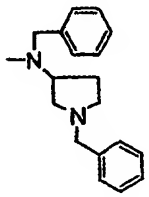
410 

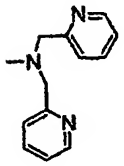
411 

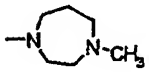
412 

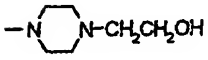
413 

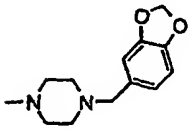
414 

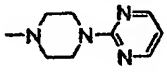
415 

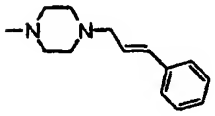
416 

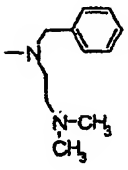
417 

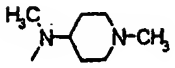
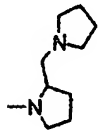
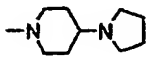
418 

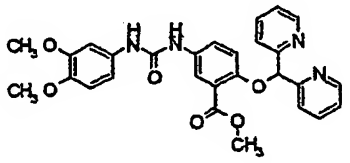
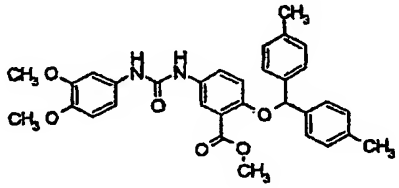
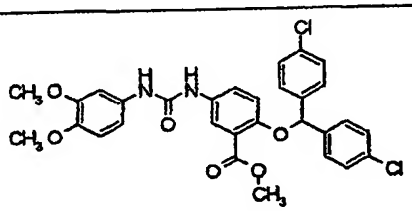
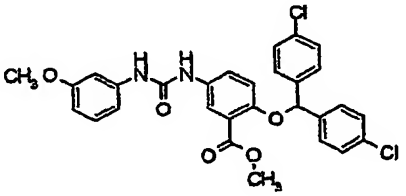
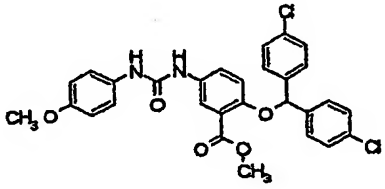
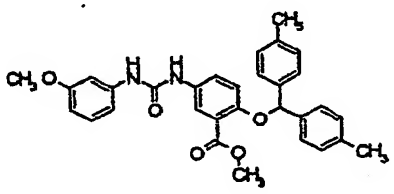
419 

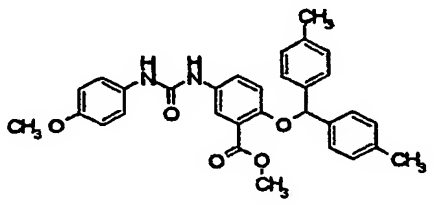
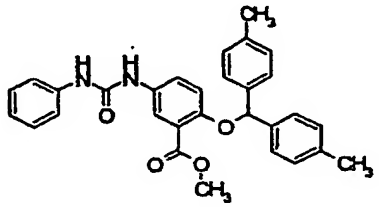
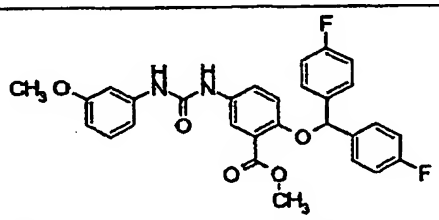
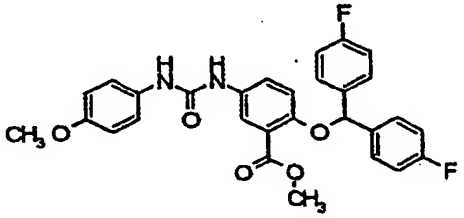
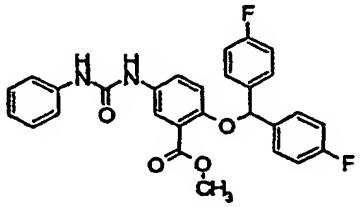
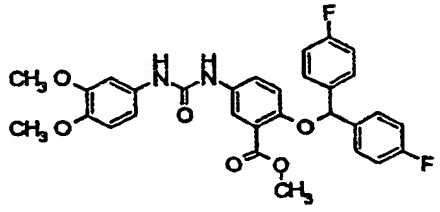
420 

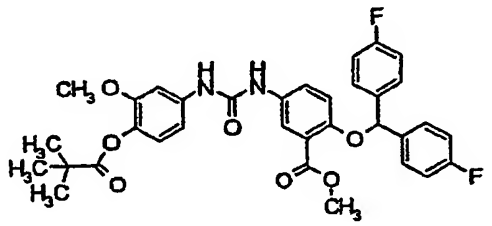
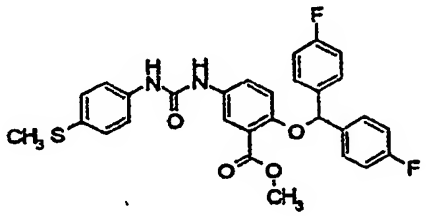
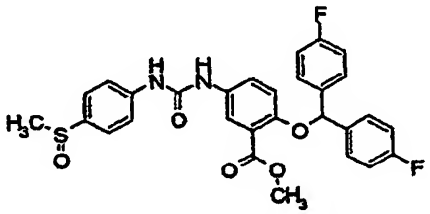
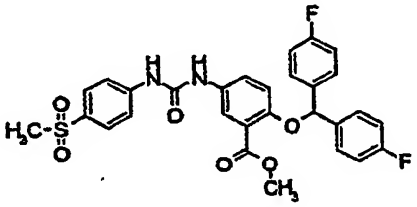
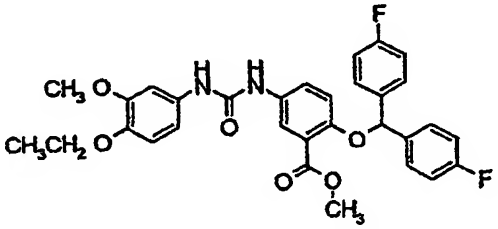
421 

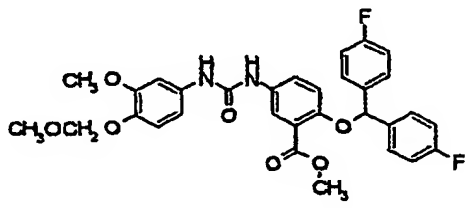
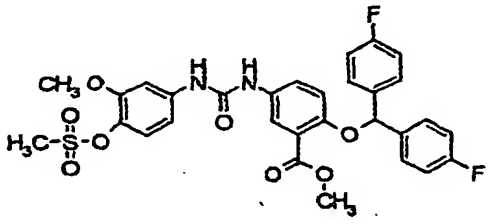
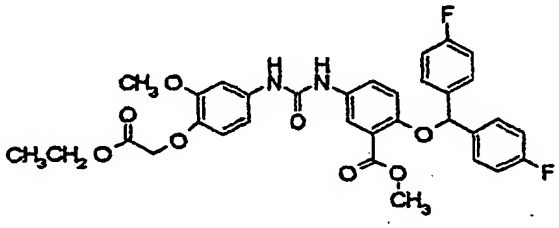
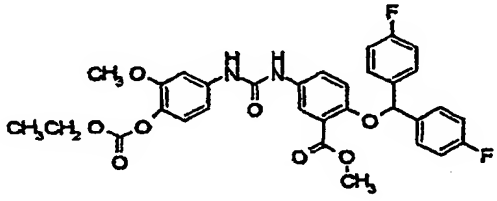
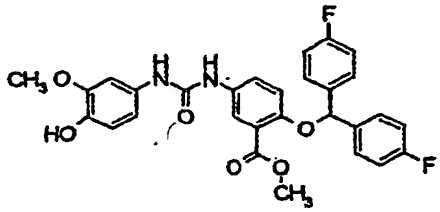
422 

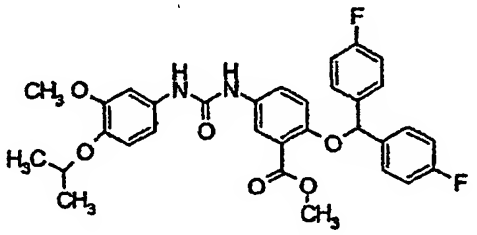
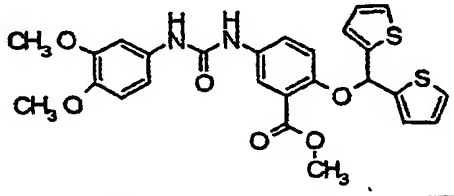
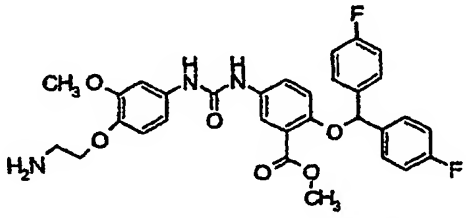
423	
424	
425	

Example No.	Structure Formula
426	
427	
428	
429	
430	
431	

432	
433	
434	
435	
436	
437	

438	
439	
440	
441	
442	

443	
444	
445	
446	
447	

448	
449	
450	

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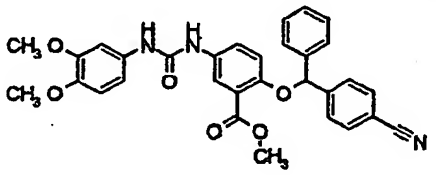
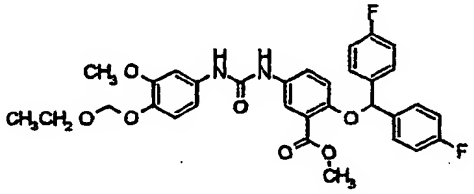
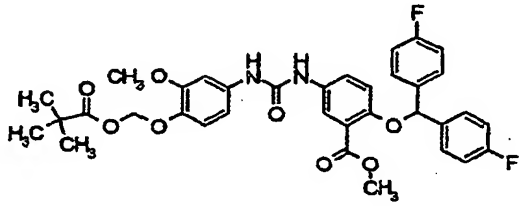
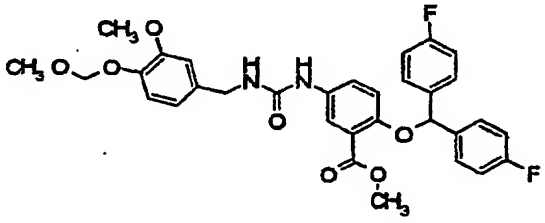
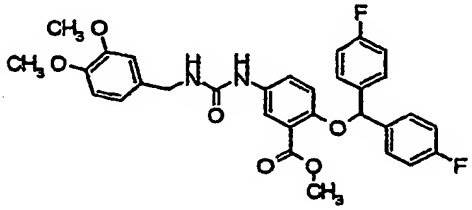
451	
452	
453	
454	
455	

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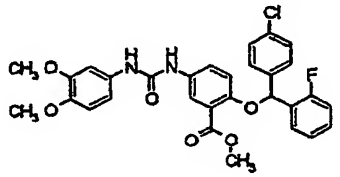
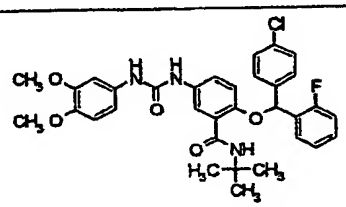
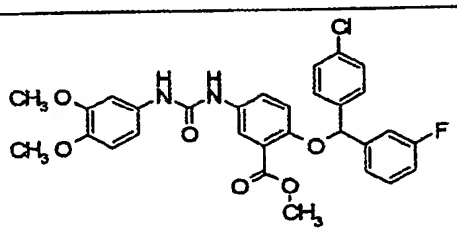
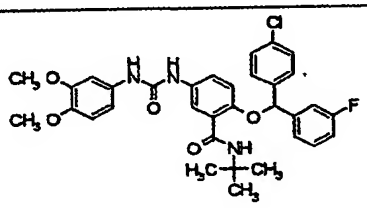
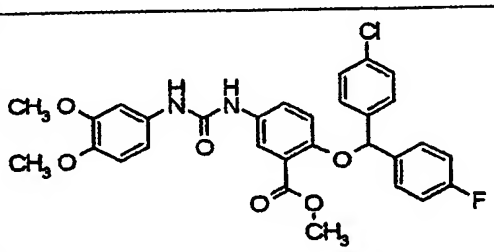
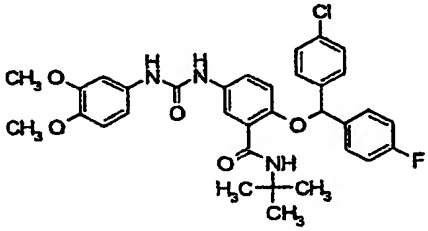
456	
457	
458	
459	
460	
461	

Test Example 1

(1) Cloning of Rat VR1

[0776] Cloning of VR1 gene was conducted by PCR method from rat brain cDNA. Using 0.5 ng of rat brain cDNA

(Takara Shuzo Co., Ltd.) as a template, PCR reaction was carried out in Gene Amp PCR System 9700 (Applied Biosystems) using KON DNA Polymerase (Toyobo Co., Ltd.) (reaction conditions: 35 cycles of treatments at 95°C for 30 seconds, at 55°C for 30 seconds and at 72°C for 2 minutes) by adding 50 pmol of primers, 5'-GGGGAATTCGCCACCATGGAACAACGGGCTAGCTTA-3' and 5'-GGGGCGGCCGCTTATTTCTCCCCTGGGACCATGGAATCCTT-3', respectively, which were prepared by referring to the base sequence of the VR1 gene reported by Caterina, M.J. et al. (Nature 389 (6653):816-24 (1997)).

(2) Preparation of Plasmid for Expression of Rat VR1

[0777] The PCR fragment obtained above was digested with restriction enzymes EcoRI (Takara Shuzo Co., Ltd.) and NotI (Takara Shuzo Co., Ltd.), and subjected to agarose gel electrophoresis to collect DNA fragment of 2.5kb. The DNA fragment and a plasmid pMSR α neo (WO 00/44756) for expression in animal cells, which was previously digested with EcoRI and NotI, were mixed and ligated by DNA Ligation Kit Ver. 2 (Takara Shuzo Co., Ltd.). Transformation of E. coli JM109 competent cells gave plasmid pRVR1.

(3) Introduction of the Plasmid for Expression of Rat VR1 into CHO-K1 Cells and Expression thereof

[0778] CHO-K1 cells (ATCC No.: CCL-61) were grown in a 150 cm^2 of cell culture flask (Corning Coaster) using Ham's F12 medium (GIBCO BRL) containing 10% fetal calf serum (GIBCO BRL) and were collected from the flask by using 0.5 g/L trypsin-0.2 g/L EDTA (GIBCO BRL). The cells were washed with PBS (GIBCO BRL), centrifuged (1000 rpm, 5 minutes) and suspended in PBS. Next, the DNA was introduced into the cells using Gene Pulser (Bio-Rad Laboratories Inc.) under the following conditions. Namely, 1×10^7 cells and 15 μg of plasmid pRVR1 for expression of rat VR1 were added into a cuvette having a 0.4 cm of gap, and electroporation was carried out under 0.25 kV of electric voltage and 960 μF of capacitance. Subsequently, the cells were transferred into Ham's F12 medium containing 10% fetal calf serum, and incubated for 24 hours. The cells were then collected, centrifuged and suspended in Ham's F12 medium containing 10% fetal calf serum and Geneticin (GIBCO BRL) at a concentration of 500 μg/ml. The suspension of cells was diluted to a concentration of 10^4 cells/mL, and inoculated on 96-well plates (Corning Coaster) to obtain Geneticin-resistant strains.

[0779] Subsequently, the resulting Geneticin-resistant strains were cultured in the 96-well plates (Corning Coaster). Next, after the medium was removed by suction, 100 μl of an assay buffer (1 mM $CaCl_2$, HBSS W/O sodium bicarbonate (GIBCO BRL), 0.5% BSA and 20 mM HEPES (Dojindo Molecular Technologies, Inc.), pH 7.5) was added to each well, and the cells were washed twice. Subsequently, 100 μl of the assay buffer containing 2.5 μCi/ml of ^{45}Ca (Daiichi Pure Chemicals) and 1 μM of capsaicin (Wako Pure Chemical Industries, Ltd.) was added to each well and the reaction was carried out for 30 minutes. After the assay buffer was removed by suction, the well plate containing the cells were washed twice with 100 μl of ice-cooled PBS (GIBCO BRL), and to each well was added 150 μl of MicroScint-20 (Packard Industry Company, Inc.) with stirring. Subsequently, the radioactivity was measured with TopCount (Packard Industry Company, Inc.) to select RVR1/CHO strains of which calcium concentration is increased when capsaicin is added to.

(4) Cloning of Human VR1

[0780] Cloning of VR1 gene was conducted by PCR method from human brain cDNA. Using 0.5ng of human brain cDNA (Clonetech Inc., Quick-Clone cDNA) as the template, PCR reaction was carried out in Gene Amp PCR System 9700 (Applied Biosystems) using KON DNA Polymerase (Toyobo Co., Ltd.) (reaction conditions: 35 cycles of treatments at 95°C for 30 seconds, at 55°C for 30 seconds and at 72°C for 2 minutes), by adding a 50 pmol of primers, 5'-GGGGAATTCGCCACCATGAAGAAATGGAGCAGCACAGACTT-3' and 5'-GGGGCGGCCGCTCACTTCTCCCCGGAAGCGGCAGGACTCTT-3', respectively, which were prepared referring to the base sequence (WO 99/37675) of the VR1 gene reported by Caterina, M.J. et al.

(5) Preparation of Plasmid for Expression of Human VR1

[0781] The PCR fragment obtained above was digested with restriction enzymes EcoRI (Takara Shuzo Co., Ltd.) and NotI (Takara Shuzo Co., Ltd.), and subjected to agarose gel electrophoresis to collect DNA fragment of 2.5kb. The DNA fragment and a plasmid pMSR α neo (WO 00/44756) for expression in animal cells, which was previously digested with EcoRI and NotI, were mixed and ligated by DNA Ligation Kit Ver. 2 (Takara Shuzo Co., Ltd.). The resulting plasmid was subjected to transformation of E. coli JM109 competent cells to obtain plasmid pHVR1.

(6) Introduction of the Plasmid for Expression of Human VR1 into CHO-K1 Cells and Expression thereof

[0782] CHO-K1 cells (ATCC No.: CCL-61) were grown in a 150 cm^2 of cell culture flask (Corning Coaster) using Ham's F12 medium (GIBCO BRL) containing 10% fetal calf serum (GIBCO BRL) and were collected by using 0.5 g/L trypsin-0.2 g/L EDTA (GIBCO BRL). The cells were washed with PBS (GIBCO BRL), centrifuged (1000 rpm, 5 minutes) and suspended in PBS. Next, DNA was introduced into the cells using Gene Pulser (Bio-Rad Laboratories Inc.) under the following conditions. Namely, 1×10^7 cells and 15 μg of plasmid pHVR1 for expression of human VR1 were added into a cuvette of a 0.4 cm gap, and electroporation was carried out at 0.25 kv of electric voltage and 960 μF of capacitance. Subsequently, the cells were transferred into Ham's F12 medium containing 10% fetal calf serum, and incubated for 24 hours. The cells were then collected, centrifuged, and then suspended in Ham's F12 medium containing 10% fetal calf serum and Geneticin (GIBCO BRL) at a concentration of 500 μg/ml. The suspension of cells was diluted to a concentration of 10^4 cells/mL, which was inoculated on 96-well plates (Corning Coaster) to obtain Geneticin-resistant strains.

[0783] Subsequently, the resulting Geneticin-resistant strains were cultured in the 96-well plates (Corning Coaster). Next, after the medium was removed by suction, 100 μl of an assay buffer (1 mM $CaCl_2$, HBSS W/O sodium bicarbonate (GIBCO BRL), 0.5% BSA and 20 mM HEPES (Dojindo Molecular Technologies, Inc.), pH 7.5) was added to each well, and the cells were washed twice. Subsequently, 100 μl of the assay buffer containing 2.5 μCi/ml of ^{45}Ca (Daiichi Pure Chemicals) and 1 μM of capsaicin (Wako Pure Chemical Industries, Ltd.) was added to each well and the reaction was carried out for 30 minutes. After the assay buffer was removed by suction, the cells were washed twice with 100 μl of ice-cooled PBS (GIBCO BRL), and to each well was added 150 μl of MicroScint-20 (Packard Industry Company, Inc.) with stirring. Subsequently, the radioactivity was determined with Top Count (Packard Industry Company, Inc.) to select HVR1/CHO strains of which calcium concentration is increased when capsaicin is added thereto.

(7) Evaluation of Compounds Based on Cell Death

[0784] Caterina, M.J. et al. (Nature 389 (6653): 816-24 (1997)) have reported that cells expressing vanilloid receptor died in the presence of capsaicin which is VR1 agonist. The compounds were evaluated based on this. RVR1/CHO and HVR1/CHO strains were inoculated on 96-well microplates (Corning Coaster) at a concentration of 4×10^4 cells/well, respectively and were cultured for 20 hours. After the culture was removed by suction, 180 μl of Ham's F12 medium (GIBCO BRL) containing 10% fetal calf serum (GIBCO BRL) was added to each well. Next, 20 μl of the assay buffer (Ham's F12 medium (GIBCO BRL), 0.5% BSA and 20 mM HEPES (Dojindo Molecular Technologies, Inc.), pH 7.5) containing a test compound at a final concentration of 1 μM was added to each well and the reaction was carried out in a carbon dioxide incubator for 3 hours. Subsequently, and Alama Blue (Wako Pure Chemical Industries, Ltd.) at a concentration of 25 μl was added to each well, and again cultured for 20 hours. Next, fluorescence was measured at excitation wavelength of 530nm and fluorescence wavelength of 590nm using multilabel counter (Wallac-Berthold, Japan), and survival rate of cell was determined.

[0785] According to the above-mentioned method, the agonist activity of test compounds was determined. As a result, the survival rate of the cells in the presence of 1 μM of the compound which was obtained in Example 2 was 0%.

Test Example 2

Mouse eye dropping test

[0786] Eight of 4-5 weeks old ICR male mice (Japan SLC) were used in a group. 0.01 mL of the drug was added dropwise to the eye, and the time when the mouse continued to close the eye was measured. The stimulation of the drug was evaluated as positive when the time is more than 10 seconds, and as negative when the time is less than 10 seconds. At 1 hour after the initial treatment, a solution of capsaicin (0.3 μg) was added dropwise to the eye to evaluate whether the stimulation is or not, and examined the desensitizing activity of the compound. The stimulating and desensitizing activity of the drug were calculated as a value of ED_{50}. The drug was dissolved in a mixture of 10% ethanol, 20% Tween and 80-70% physiological salt solution.

[0787] ED_{50} of the compound obtained in Example 2 was 2.2 μg.

Test Example 3

Tail-flick test

[0788] Four to five weeks old ICR male mice (Japan SLC) were used in this test. The mouse was put into a retainer, the tail end was dipped into 55°C water bath, and the time until the tail end rose to the surface was measured. The

time was previously measured before the administration of the drug, and the mouse having the time of less than 2 seconds were selected and used in the test. Cut-off time was set to 10 seconds. The drug was administered subcutaneously, and the time was measured after 1, 3 and 6 hours to evaluate the effects of the drug. The drug was dissolved in a mixture of 10% ethanol, 20% Tween and 80-70% physiological salt solution.

[0789] Minimum effective dose of the compound obtained in Example 2 was 1 mg/Kg.

Test Example 4

Measurement of mouse bladder volume

[0790] Five weeks old ICR male mice were used in this test. At 3 hours after the subcutaneous administration of the drug, the abdomen of mouse was cut open under urethane anesthesia (30 mg/mouse) to expose the bladder. Physiological salt solution was infused into the bladder at the rate of 0.05mL/minutes to check excretion reflection. All of the urine was drained off, and the physiological salt solution was infused again, and then, the bladder volume of mouse was calculated by measuring the time to urination. The results are shown in Table 2.

[0791] Resiniferatoxin (RTX) and the compound obtained in Example 22 increased significantly the bladder volume of the mouse.

Table 2

The influence of RTX and the compound obtained in Example 22 on the bladder volume of a mouse anesthetized with urethane

Compound	Dose (mg/kg, sc)	N	Bladder volume (mL)
Vehicle	-	14	0.12 ± 0.01
RTX	0.03	8	0.24 ± 0.04
	0.1	8	0.39 ± 0.04*
Example 22	3	6	0.17 ± 0.03
	10	7	0.28 ± 0.05*
	100	8	0.31 ± 0.06**

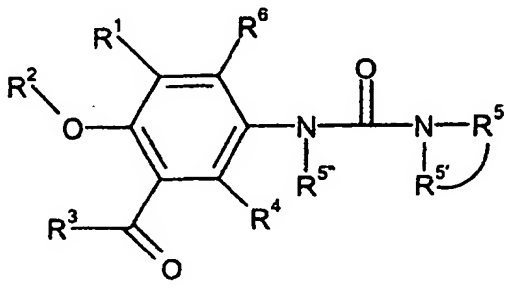
Mean ± S.E. * $p \leq 0.05$, ** $p \leq 0.01$ vs. vehicle (Dunnett's test).

Industrial Applicability

[0792] The present invention provides novel benzene derivatives which have vanilloid receptor agonist activity and are useful as a drug such as an analgesic and an agent for preventing and/or treating urinary frequency and/or urinary incontinence.

Claims

1. A compound represented by the formula (I):



(I)

wherein R^1, R^4 and R^6 each independently represents a hydrogen atom, a halogen atom or an optionally substituted hydrocarbon group;

R^2 represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

R^3 represents an optionally substituted hydrocarbon group, $NR^{7'}R^7$ or OR^8 (wherein $R^{7'}$ represents a hydrogen atom or an optionally substituted hydrocarbon group, and R^7 represents an optionally substituted non-aromatic group, or $R^{7'}$ and R^7 may form an optionally substituted ring together with the adjacent nitrogen atom, and R^8 represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group);

R^5 represents an optionally substituted hydrocarbon group (except for an optionally substituted benzoyl group) or an optionally substituted heterocyclic group (except for a quinolyl group); $R^{5'}$ represents a hydrogen atom, or an optionally substituted hydrocarbon group, or R^5 and $R^{5'}$ may form an optionally substituted ring together with the adjacent nitrogen atom; and $R^{5''}$ represents a hydrogen atom or an optionally substituted hydrocarbon group; or

a salt thereof.

2. The compound according to claim 1, wherein the optionally substituted hydrocarbon group represented by R^1, R^2, R^3, R^4, R^5, $R^{5'}$, $R^{5''}$, R^6, $R^{7'}$ and R^8 each independently represents a C_{1-6}alkyl group, a C_{2-6}alkenyl group, a C_{2-6}alkynyl group, a C_{3-10}cycloalkyl group, a C_{3-10}cycloalkenyl group, a C_{4-12}cycloalkylalkyl group, a C_{4-12}cycloalkenylalkyl group, a C_{6-14}aryl group or a C_{7-19}aralkyl group, which may be independently substituted;

the optionally substituted non-aromatic group represented by R^7 represents a C_{1-6}alkyl group, a C_{2-6}alkenyl group, a C_{2-6}alkynyl group, a C_{3-10}cycloalkyl group, a C_{3-10}cycloalkenyl group, a C_{4-12}cycloalkylalkyl group, a C_{4-12}cycloalkenylalkyl group, a C_{7-19}aralkyl group, or a 5- to 12-membered non-aromatic heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may be independently substituted;

the optionally substituted heterocyclic group represented by R^2, R^5 and R^8 each independently represents a 5- to 12-membered aromatic heterocyclic group, or a saturated or unsaturated non-aromatic heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, which may be substituted; and

the ring formed by $R^{7'}$ and R^7, and R^5 and $R^{5'}$ together with the adjacent nitrogen atom, represents an optionally substituted 3- to 12-membered nitrogen-containing heterocyclic ring which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atoms and one nitrogen atom.

3. The compound according to claim 1 or 2, wherein the substituents are 1 to 4 groups selected from a halogen atom; a nitro group; a cyano group; a hydroxy group; a mercapto group; a sulfo group; a sulfino group; a phosphono group; an optionally halogenated C_{1-6}alkyl group; an oxo group; an amidino group; an imino group; a C_{1-4}alkylenedioxy group; an optionally halogenated C_{1-6}alkoxy group; an optionally halogenated C_{1-6}alkylthio group; a carboxyl group; a formyl group; an optionally halogenated C_{1-6}alkyl-carbonyl group; a formyloxy group; an optionally halogenated C_{1-6}alkyl-carbonyloxy group; an optionally halogenated C_{1-6}alkoxy-carbonyl; a C_{7-11}aralkyl group; a C_{7-11}aralkyloxy group; a C_{7-11}aralkyloxy-carbonyl group; a thiocarbamoyl group; an optionally halogenated C_{1-6}alkylsulfinyl group; an optionally halogenated C_{1-6}alkylsulfonyl group; a sulfamoyl group; an optionally halogenated mono-C_{1-6}alkylsulfamoyl group; an optionally halogenated di-C_{1-6}alkylsulfamoyl group; a C_{6-10}arylsulfamoyl group; a C_{6-10}aryl group; a C_{6-10}aryloxy group; a C_{6-10}arylthio group; a C_{6-10}arylsulfinyl group; a C_{6-10}arylsulfonyl group; a C_{6-10}aryl-carbonyl group; a C_{6-10}aryl-carbonyloxy group; a group represented by the formula $-CONR^9R^{10}$ (wherein R^9 and R^{10} each represents (1) a hydrogen atom, (2) a C_{1-6}alkyl group which may have 1 to 4 substituents selected from a halogen atom and a hydroxy group, (3) a C_{6-10}aryl group which may have 1 to 4 substituents selected from a halogen atom, a hydroxy group, and an optionally halogenated C_{1-6}alkyl group or (4) a 5- to 12-membered heterocyclic group which may have 1 to 4 substituents selected from a halogen atom and an optionally halogenated C_{1-6}alkyl group, containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms, or R^9 and R^{10} may form with the adjacent nitrogen atom a 3- to 8-membered nitrogen-containing heterocyclic ring which may contain 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom in addition to carbon atom and one nitrogen atom); a group represented by the formula $-NR^9R^{10}$ (wherein R^9 and R^{10} are as defined above); a group represented by the formula $-NHCONR^9R^{10}$ (wherein R^9 and R^{10} are as defined above); a group represented by the formula $-NR^9COR^{10}$ (wherein R^9 and R^{10} are as defined above); a group represented by the formula $-NR^9SO_2R^{10}$ (wherein R^9 and R^{10} are as defined above); and a 5- to 12-membered heterocyclic group containing 1 to 4 hetero atoms consisting of 1 to 3 kinds of hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom as ring-constituting atoms.

4. The compound according to claim 1, wherein R^1 represents a hydrogen atom; R^4 represents a hydrogen atom or

an optionally halogenated C_{1-4}alkyl group; and R^6 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group.

5. The compound according to claim 1, wherein R^2 represents a C_{7-19}aralkyl group which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di-C_{6-10}arylsulfamoyl group.

6. The compound according to claim 1, wherein R^2 represents a C_{7-19}aralkyl group which may have 1 to 4 substituents selected from a halogen atom, an optionally halogenated C_{1-4}alkyl group, a nitro group, a cyano group, and a C_{1-4}alkoxy-carbonyl group.

7. The compound according to claim 6, wherein the C_{7-19}aralkyl group is a benzhydryl group.

8. The compound according to claim 1, wherein R^3 represents a C_{1-4}alkyl group, a C_{1-4}alkylamino group or C_{1-4}alkoxy group.

9. The compound according to claim 1, wherein R^5 represents a C_{6-10}aryl group, a pyridyl group or a C_{7-11}aralkyl group, each of which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxycarbonyl group, an optionally halogenated C_{1-6}alkylthiocarbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-C_{6-10}arylsulfamoyl group, and a di-C_{6-10}arylsulfamoyl group.

10. The compound according to claim 1, wherein R^5 represents a phenyl group which may have 1 or 2 C_{1-6}alkoxy groups.

11. The compound according to claim 1, wherein R^1 represents a hydrogen atom; R^2 represents a C_{7-19}aralkyl group which may have 1 to 4 substituents selected from a halogen atom, an optionally halogenated C_{1-4}alkyl group, a nitro group, a cyano group, and a C_{1-4}alkoxy-carbonyl group; R^3 represents a C_{1-4}alkyl group, a C_{1-4}alkylamino group or C_{1-4}alkoxy group; R^4 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group; R^5 represents a C_{6-10}aryl group, a pyridyl group or a C_{7-11} aralkyl group, each of which may have 1 to 4 substituents selected from an optionally halogenated C_{1-6}alkyl group, a halogen atom, a nitro group, a cyano group, a carboxyl group, an amino group, an optionally halogenated C_{1-6}alkyl-carbonyl group, a C_{6-10}aryl-carbonyl group, an optionally halogenated C_{1-6}alkylthio group, an optionally halogenated C_{1-6}alkoxy group, a C_{6-10}aryl group, a C_{6-10}aryloxy group, a C_{6-10}arylthio group, an optionally halogenated C_{1-6}alkoxy-carbonyl group, an optionally halogenated C_{1-6}alkylthio-carbonyl group, an optionally halogenated C_{1-6}alkylsulfinyl group, an optionally halogenated C_{1-6}alkylsulfonyl group, an optionally halogenated mono-C_{1-6}alkylsulfamoyl group, an optionally halogenated di-C_{1-6}alkylsulfamoyl group, a C_{6-10}arylsulfinyl group, a C_{6-10}arylsulfonyl group, a mono-$C_{6-10aryl}$sulfamoyl group, and a di C_{6-10}arylsulfamoyl group; and R^6 represents a hydrogen atom or an optionally halogenated C_{1-4}alkyl group.

12. The compound according to claim 1, wherein $R^{5'}$, $R^{5''}$, and $R^{7'}$ each represents a hydrogen atom.

13. The compound according to claim 1, which is N-(4-benzhydryloxy-3-isobutyrylphenyl)-N'-(3,4-dimethoxyphenyl) urea,

methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-fluorophenyl)(phenyl)methoxy]benzoate,

methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(4-trifluoromethylphenyl)(phenyl)methoxy]benzoate,

methyl 5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-[(2-chlorophenyl)(4'-chlorophenyl)methoxy] benzoate,

N-(tert-butyl)-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)-2-{phenyl[4-(trifluoromethyl)phenyl]methoxy}benzamide,

methyl 2-[(3,4-difluorophenyl)(phenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate,

methyl 2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzoate,

N-(tert-butyl)-2-{(2-chlorophenyl)[4-(trifluoromethyl)phenyl]methoxy}-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide,

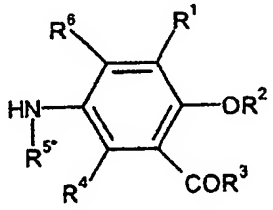
N-(tert-butyl)-2-[(4-chlorophenyl)(2-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide,

N-(tert-butyl)-2-[(4-chlorophenyl)(3-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide, or

N-(tert-butyl)-2-[(4-chlorophenyl)(4-fluorophenyl)methoxy]-5-({[(3,4-dimethoxyphenyl)amino]carbonyl}amino)benzamide.

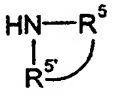
14. A prodrug of the compound according to claim 1 or a salt thereof.

15. A process for preparing the compound according to claim 1 or a salt thereof, which comprises subjecting a compound represented by the formula:



(II)

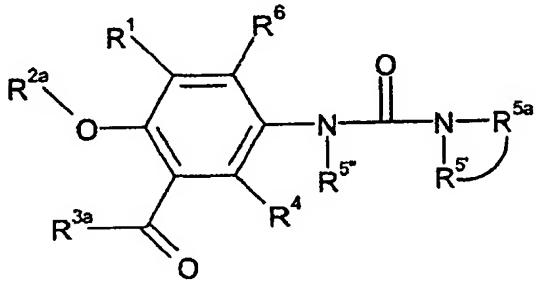
wherein each symbol is as defined in claim 1, or a salt thereof and a compound represented by the formula:



wherein each symbol is as defined in claim 1, or a salt thereof to urea synthesis reaction.

16. A pharmaceutical composition comprising the compound according to claim 1, a pharmaceutically acceptable salt thereof or a prodrug thereof.

17. A vanilloid receptor 'agonist comprising a compound represented by the formula:



(Ia)

wherein R^1, R^4 and R^6 each independently represents a hydrogen atom, a halogen atom or an optionally substituted hydrocarbon group;

R^{2a} represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

R^{3a} represents an optionally substituted hydrocarbon group, $NR^{7'}R^{7a}$ or OR^{8} (wherein $R^{7'}$ represents a hydrogen atom or an optionally substituted hydrocarbon group, R^{7a} and R^{8} each independently represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or $R^{7'}$ and R^{7a} may form an optionally substituted ring with the adjacent nitrogen atom);

R^{5a} represents an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

$R^{5'}$ represents a hydrogen atom, or an optionally substituted hydrocarbon group, or R^{5a} and $R^{5'}$ may form an optionally substituted ring with the adjacent nitrogen atom;

$R^{5''}$ represents a hydrogen atom or an optionally substituted hydrocarbon group,

a pharmaceutically acceptable salt thereof or a prodrug thereof.

18. An agent for preventing and/or treating urinary frequency and/or urinary incontinence, which comprises the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof.

19. An analgesic which comprises the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof.

20. Use of the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof for manufacturing an agent for preventing and/or treating urinary frequency and/or urinary incontinence.

21. Use of the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof for manufacturing an analgesic.

22. Use of the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof for manufacturing a vanilloid receptor agonist.

23. A method for preventing and/or treating urinary frequency and/or urinary incontinence, which comprises administrating an effective amount of the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof to a mammal.

24. An analgesic method which comprises administrating an effective amount of the compound of the formula (Ia) according to claim 17, a pharmaceutically acceptable salt thereof or a prodrug thereof to a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09995

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C275/38, 275/42, C07D213/30, 213/40, 213/65, 213/75, 261/14, 295/20, 317/58, 317/66, 319/18, 321/10, A61K31/17, 31/216, 31/357, 31/36, 31/4045, 31/4184, 31/42, 31/44,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C275/38, 275/42, C07D213/30, 213/40, 213/65, 213/75, 261/14, 295/20, 317/58, 317/66, 319/18, 321/10, A61K31/17, 31/216, 31/357, 31/36, 31/4045, 31/4184, 31/42, 31/44,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN(CA, REGISTRY)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 135162 A2 (Lindner, Wolfgang, Dr.), 27 March, 1985 (27.03.85), Full text & JP 60-48954 A & US 4652762 A	1,2,4,8,9, 12
X	JP 6-80911 A (Nitto Denko Corp.), 22 March, 1994 (22.03.94), Example 9 (Family: none)	1,2,4,8,9, 12
X	DE 2458624 A1 (Lentia GmbH., Chem. u. pharm. Erzeugnisse-Industriebedarf), 11 December, 1974 (11.12.74), Full text & JP 51-125247 A & JP 50-95246 A	1-4,8,9,12, 14,16

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October, 2002 (31.10.02)	19 November, 2002 (19.11.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09995

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	W. LINDNER, Ch. LEITNER, G. URAY, "LIQUID CHROMATOGRAPHIC SEPARATION OF ENANTIOMERIC ALKANOLAMINES VIA DIASTEREOMERIC TARTARIC ACID MONOESTERS", Journal of Chromatography, 1984, Vol.316, pages 605 to 616	1,2,4,8,9
X	VON G. ZOELSS, "Zur synthese des kardioselektiven β-Rezeptoren-Blockers Celiprolol", Arzneimittel-forschung, 1983, Vol.33, No.1A, pages 2 to 4	1-4,8,9
X	Nobuyoshi SUMI, Yasuyuki NISHIGUCHI, Naotaka TERADA, Nobuyoshi HAGIDAI, Akira NOMURA, "Celiprolol no Taisha Sanbutsu, Bunkaibutsu, Kyozatsubutsu, Kogaku Iseitai no Mouth ni okeru Kyusei Dokusei Shiken", Pharmacometrics, 1989, Vol.38, No.4, pages 295 to 303	1-4,8,9,12, 14,16
X	VON O. HOFER, K. SCHLOEGL, "Absolute Konfiguration und Enantiomere reinheit von Celiprolol", Arzneimittel-Forschung, 1986, Vol.36, No.8, pages 1157 to 1161	1-4,8,9
X	ABDULRAHMAN A. ALMOTREFI, NDUNA DZIMIRI, HASSAN Y. ABOUL-ENEIN, LOUIS S. PREMKUMAR, "SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF THE ANTIFIBRILLATORY EFFECT OF FLUORINATED DERIVATIVES OF CARAZOLOL AND CERIPROLOL:COMPARISON WITH PROPRANOLOL", General Pharmacology, 1993, Vol.24, No.3, pages 721 to 725	1-4,8,9,14, 16
X	THOMAS J. DIFEO, JUDITH E. SHUSTER, "Determination of a prosess intermediate of celiprolol and its potential impurities by gradient high-perfomance liquid chromatography-appriction of high-low chromatography", Journal of Pharmaceutical & Biomedical Analysis, 1991, Vol.9, Nos.10 to 12, pages 823 to 828	1-6,8,9,12
X	L. H. SMITH, "β-Adrenergic Blocking Agents. 15. 1-Substituted Ureidophenoxy-3-amino-2-propanols", Journal of Medicinal Chemistry, 1977, Vol.20, No.5, pages 705 to 708	1-4,8,9,12, 14,16
X	NORBERT M. MAIER, GEORG URAY, "Efficient high-performance liquid chromatographic enantioseparation of five-memberd aryl-substituted lactones and cyclic carbamates on a (R, R)-diaminodihydroethanoanthracene-derived chiral stationary phase", Journal of Chromatography A, 1996, Vol.740, No.1, pages 11 to 19	1,2,4,8,9
A	WO 00/47577 A1 (SMITHKLINE BEECHAM PLC), 17 August, 2000 (17.08.00), & JP 2002-536445 A & EP 1150977 A1	1-22

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09995

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23, 24
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 23 and 24 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required to search (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. [X] Claims Nos.: 1-12, 14-22
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Parts of claims 1-12 and 14-22 are inadequately supported by the description, so that relevant prior art cannot be specified.
(continued to extra sheet)

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09995

Continuation of Box No.I-2 of continuation of first sheet(1)

Claim 1 and so on include compounds which are not concretely disclosed in the description and are much different from the compounds concretely disclosed in the description in chemical structure, functional group, or the like (for example, compounds wherein R^1, R^4 and R^6 are each a group bearing a fused aromatic ring) (hereinafter referred to as "undisclosed compounds").

Because of the common general technical knowledge that the compounds capable of interacting with a receptor are generally limited in structure, volume, functional groups, hydrophilicity, hydrophobicity, and so on, however, it cannot be presumed that the undisclosed compounds as well as the compounds concretely disclosed in the description may exhibit vanilloid receptor agonism.

Thus, the undisclosed compounds are inadequately supported in respect of usefulness as vanilloid receptor agonist.

As to the undisclosed compounds, therefore, no meaningful opinion can be formed on the relevance to prior art (particularly on the inventive step to be examined in consideration of action and effect).

This international search report covers only the following compounds including those disclosed in Example of the description, processes for the preparation thereof and medicines containing the compounds:

compounds represented by the general formula (I) wherein R^1, R^4, R^6 and $R^{5'}$ are each hydrogen; OR^2 is -O-C···C (wherein the symbol "C···C" is a part of an optionally substituted hydrocarbon or heterocyclic group and the bond "···"is a double or triple bond); R^3 is alkyl, alkoxy, or N-C-C (wherein the symbol "C-C" is a part of an optionally substituted hydrocarbon group); R^5 is "C··· an atom other than hydrogen", which is a part of an optionally substituted hydrocarbon or heterocyclic group (wherein the bond "···" is a double or triple bond) and $R^{5'}$ is "C···an atom other than hydrogen", which is a part of an optionally substituted hydrocarbon or heterocyclic group (wherein the bond "···" is a double or triple bond).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09995

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

Int.Cl[7] 31/4409, 31/445, 31/4453, 31/4468, 31/495, 31/55, 31/551, A61P1/06, 1/08, 1/14, 3/04, 3/06, 3/08, 9/00, 9/02, 9/10, 11/02, 13/02, 15/12, 17/00, 17/04, 17/06, 19/02, 25/00, 25/02, A61P25/06, 25/16, 29/00, 31/04, 31/18, 35/00, 37/08, 43/00

(According to International Patent Classification (IPC) or to both national classification and IPC)

Continuation of B. FIELDS SEARCHED
Minimum Documentation Searched(International Patent Classification (IPC))

Int.Cl[7] 31/4409, 31/445, 31/4453, 31/4468, 31/495, 31/55, 31/551, A61P1/06, 1/08, 1/14, 3/04, 3/06, 3/08, 9/00, 9/02, 9/10, 11/02, 13/02, 15/12, 17/00, 17/04, 17/06, 19/02, 25/00, 25/02, A61P25/06, 25/16, 29/00, 31/04, 31/18, 35/00, 37/08, 43/00

Minimum documentation searched (classification system followed by classification symbols)

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